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THE PHYSIOLOGY
OF THE
NEWBORN INFANT

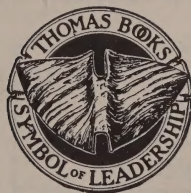
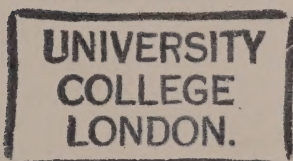
THE PHYSIOLOGY OF THE NEWBORN INFANT

By

CLEMENT A. SMITH, M.D.

*Assistant Professor of Pediatrics, Harvard Medical School
Director of Research on the Newborn Infant
Boston Lying-in Hospital*

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TO
MARGARET EARHART SMITH

FOREWORD

AS soon as the baby is born and its umbilical cord is tied and cut, it no longer subsists as a biological parasite; it becomes at that instant a separate individual both physiologically and legally. Oliver Wendell Holmes, in his happy fashion, thus celebrates this event:

“So the stout fetus, kicking and alive,
Leaps from the fundus for his final dive.
Tired of the prison where his legs were curled,
He pants, like Rasselas, for a wider world.
No more to him their wonted joys afford
The fringed placenta and the knotted cord.”

As the following pages indicate, never in the later life of man do such climactic changes occur in so short a time. The onset of puberty is gradual, the period of senescence consumes many years, even death itself for some may be a lingering event; a few seconds, however, suffice for the first breath, the adequate expansion of the lungs, and the adjustment of the circulation to pulmonary respiration. Other adaptations, such as the maintenance of body temperature, the establishment of digestion, and the regulation of metabolism and water balance, are completed in a few days. Not only pediatricians but obstetricians also should know what these changes are and how they occur, so that they may recognize the difference between the abnormal and the normal in their smallest patients. Above all they should recognize that the newborn infant presents certain problems of its own and that it is not merely a very young baby.

Dr. Clement Smith has been a friend and colleague of mine for many years; thus I have been privileged to witness the conception and the early development of this book—which I believe is unique in its field—as well as some of the investigative work which it describes. It reflects his characteristic scientific attitude and verbal clarity, and I hope that its content will prove as helpful and instructive to its other readers as it has to me.

FREDERICK C. IRVING, M.D.

William Lambert Richardson Professor of
Obstetrics, Harvard University

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Authors and publishers who have allowed the reproduction of their own illustrations are named individually underneath the various figures; their interest and generosity are collectively acknowledged here.

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CONTENTS

Foreword	vii
Acknowledgment	ix
Chapter I. Introductory	3
Chapter II. Respiration: Fetal Aspects	7
Section 1. Respiratory Activity before Birth	7
2. Fetal Activity in Relation to the Gas Content of Fetal Blood	13
3. Oxygen and Carbon Dioxide Economy of the Human Fetus	18
4. Respiratory Peculiarities of the Fetal Blood	22
5. Clinical Summary	28
Chapter III. Respiration: Neonatal Aspects	33
Section 1. The Onset of Breathing at Birth	33
2. Effects and Duration of Anoxia at Birth	35
3. The Physical State of the Neonatal Lung	39
4. Mechanical Forces in Early Respiration	42
5. Clinical Manifestations of Respiratory Adjustment after Birth	45
6. Rate, Volume, and Regularity of Breathing in the Neonatal Period	50
7. Clinical Summary	57
Chapter IV. The Circulatory System	63
Section 1. The Fetal Circulation and its Alterations at Birth	63
2. The Umbilical Vessels at Birth	70
3. The Fetal and Neonatal Blood Volume	73
4. The Heart and Vascular System	77
5. The Dynamics of Circulation	86
6. Fetal and Neonatal Blood Pressures	91
7. Clinical Summary	96
Chapter V. The Blood	103
Section 1. The Erythrocytes: Number and Development	103
2. The Erythrocytes: Hemoglobin Content and Other Characteristics	110
3. The White Blood Cells	113
4. Peculiarities of Blood Coagulation in Neonatal Life	116
5. Clinical Summary	120
Chapter VI. Icterus Neonatorum	126
Chapter VII. Metabolism and Heat Regulation	138
Section 1. Energy Metabolism	138
2. Body Temperature	153
3. Clinical Summary	161

Chapter VIII. The Physiology of the Digestive Tract	166
Section 1. Functional Anatomy.....	166
2. Fetal and Neonatal Digestive Secretions.....	173
3. Clinical Summary.....	182
Chapter IX. Fetal and Neonatal Nutrition: Assimilation and Metabolism of Specific Food Substances	187
Section 1. Proteins, and the Metabolism of Nitrogenous Substances in General.....	187
2. Carbohydrate Assimilation and Metabolism.....	200
3. Fat Assimilation and Metabolism.....	207
4. Clinical Summary.....	214
Chapter X. The Assimilation and Metabolism of Minerals and Vitamins	221
Section 1. Mineral Metabolism.....	221
2. Vitamin Metabolism.....	231
3. Clinical Summary.....	237
Chapter XI. Renal Physiology: Regulation of Electrolytes and Water ...	243
Section 1. Renal Function in Neonatal Life.....	243
2. Control of Electrolytes and Water.....	250
3. Clinical Summary.....	255
Chapter XII. Neonatal Endocrinology	260
Section 1. The Sex Hormones.....	260
2. The Adrenal, Thyroid, Pancreatic, and Parathyroid Hormones.....	266
3. Clinical Summary.....	274
Chapter XIII. Neonatal Immunology	280
Index	299

THE PHYSIOLOGY
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Chapter I

INTRODUCTORY

"SOME Divines count Adam thirty years old at his Creation, because they suppose him created in the perfect age and stature of man. And surely we are all out of the computation of our age, and every man is some months older than he bethinks him; for we live, move, have a being, and are subject to the actions of the elements, and the malice of diseases, in that other World, the truest Microcosm, the Womb of our Mother. . . . In that obscure World . . . , our time is short, computed by the Moon, yet longer than the days of many creatures that behold the Sun; our selves being not yet without life, sense, and reason; though for the manifestation of its actions, it awaits the opportunity of objects, and seems to live there but in its root and soul of vegetation. Enttring afterwards upon the scene of the World, we arise up and become another creature."

Thus, a little more than three centuries ago, wrote a physician who said that his philosophy had been changed into divinity (by "those strange and mystical transmigrations that I have observed in Silk-worms"). The early parts of human life mentioned by the author of the *Religio Medici* have aroused the curiosity of others before and since his time, and the period in which "we arise up and become another creature" has been shown the occasion of perhaps more surprising changes and of certainly more numerous ones than even a Browne might have suspected. Growth of knowledge in the general territory of physiology increases the interest in its special fields, and the opportunities for understanding them. This is particularly true of those periods during which life is more dynamic than static. In no other brief span of existence can such profound alterations and adjustments be studied as in the weeks, or even the days or hours following birth.

Curiosity as to these alterations and adjustments is one origin of this book. It has not been the author's intention to dwell at too great length upon life in "that other world, the truest microcosm," nevertheless most of the subsequent chapters open with some account of the embryonic and fetal origins of the processes under particular consideration. Perhaps too much is said about them. But it is necessary to begin somewhere near the beginning, which is certainly not the moment of parturition. The threads of biological continuity cannot be taken up at unattached and unrelated ends (which, indeed, they do not naturally possess), without regard to

the living fabric of integration in which some of them fulfilled as essential a function before birth as after they became rewoven into another pattern. It is also necessary to understand what we can of the difficulties confronting prematurely born infants, and this obviously calls for some grounding in the developments of fetal existence.

The subject of neonatal physiology not only arouses interest because of the rapidly changing activities under study. In certain regards it presents other unique features. Among these is the obvious helplessness of the newborn organism in the demands of a world calling for still more adaptations than the mere forsaking of one environment for another. To understand the fundamentals of its life is the first step in helping it to survive.

Then there is the simple matter of size. Newborn infants are at that end of the size scale where absolute differences, not ordinarily very significant to larger organisms, become of relatively great importance. Thus premature infants, although only some three or four pounds lighter than those born at term, are actually only one-half as large. And in this matter (other aspects of which have been entertainingly discussed by Haldane¹), factors of body surface begin to influence heat loss, respiration, and other fundamental problems of living by a considerable degree, and to produce effects sometimes very striking when viewed by that usual standard of physiological reference, the 70 Kilo man. Moreover, the mere ingenuity and delicacy of small mechanisms has its interesting aspects. To take another sentence from the same source quoted before: "*Ruder heads stand amazed at those prodigious pieces of Nature, Whales, Elephants, Dromidaries, and Camels; these, I confess, are the Collossus and majestic pieces of her hand; but in these narrow Engines there is more curious Mathematicks; and the civility of these little Citizens more neatly sets forth the Wisdom of their Maker.*"

The physiology of newborn life is a unique field because of the alterations under way at the time, and because of the peculiarities introduced by the size of its subjects. It is also worth presenting for a perhaps less academic reason. This is the increasing relative importance of the neonatal period as a time of potential mortality. More human beings die during the first year after their birth than during any year thereafter until the period of so-called degenerative disease begins. Sometime ago Clifford² showed how the infant mortality rate (deaths during the first year per 1000 live births) in the state of Massachusetts had undergone a decline from about 132 in 1910 to a figure slightly over 50 in 1933. But by breaking down the statistics he was able to show further that this gratifying reduction

was almost entirely brought about by a great decrease in deaths among infants aged from one month to one year. The mortality in younger infants, particularly in those aged less than 14 days, had scarcely altered at all. Thus, in 1910, this neonatal period of two weeks furnished only about 25 per cent of all the first year's fatalities; in 1933 it furnished about 60 per cent. No important evidence has since appeared to show that the saving of infant life does not continue to be a problem centering upon the newborn period. Moreover, the perils which infants face during and immediately after birth are not especially those of infection; they are difficulties in the onset of respiration, handicaps brought about by congenital abnormalities, hazards of obstetrical accidents, and other situations the alleviation of which depends in great part upon an understanding of normal physiology. Therefore it is hoped that a reference work of this sort may be of aid in an increasingly important region of Pediatrics and Public Health.

One drawback to the study of fetal and neonatal life in human infants is the difficulty, or impossibility, of carrying out all the various measurements and determinations which might increase our knowledge. While the investigator in general physiology can often be his own experimental animal (or prevail for this purpose upon his hardier associates and more trusting students), he obviously must limit himself rather strictly to observation, inference, and the pathology of abnormal subjects when it comes to the exploration of problems raised by the newborn infant. Although little babies, being rather dormant organisms, are very suitable candidates for balance studies of nutrition, even in such studies, as well as in those requiring frequent measurements made upon blood samples, investigation comes up against understandable difficulties. The umbilical vessels do offer a unique source of blood for analyses, but the results obtained therefrom are a little too limited to an especially transient state of affairs to throw much light on the whole period. The investigator must therefore often turn to laboratory animals for answers to his questions. Here one is brought up against obstacles in the way of interpretation which ought to be honestly faced before the data obtained, for example, from a newborn rabbit can be used to explain what happens at the same time in the life of a human infant, or even of a newborn lamb. For one thing it is *not* the same time, because of the great differences in gestational age and maturity in the various species mentioned. From other aspects, there are differences in placental structure and in the number of fetuses sharing the uterus; both considerations call for caution in drawing wide conclusions.

One would prefer not to include any evidence from animal studies in a review which is intended more for physicians than for biologists, yet such data do have a place, and a relatively important one, in our available knowledge. However, occasional warnings are given in the following pages against their too ready acceptance as universal truths, and an attempt has been made at the end of each chapter to summarize the preceding information most properly applicable to human infants and therefore of greatest clinical usefulness.

The absence of a section devoted to the nervous system is not an oversight. Most of the available knowledge upon that subject (valuable as it is) either is limited to the fetus,³ or is anatomical in nature,⁴ or considers the newborn period only briefly in relationship to general neuromuscular development.⁵ Therefore, since it was found impossible to deal with the subject in the same way as the other aspects of neonatal physiology are treated, it has intentionally been omitted.

BIBLIOGRAPHY

1. HALDANE, J. B. S.: *Possible Worlds*, New York, Harper and Brothers, 1928.
2. CLIFFORD, S. H.: A study of neonatal mortality, *J. Pediat.* 8: 367, 1936.
3. WINDLE, W. F.: *Physiology of the Fetus; Origin and Extent of Function in Prenatal Life*, Philadelphia, W. B. Saunders Company, 1940.
4. CONEL, J. LEROY: *The Post-natal Development of the Human Cerebral Cortex*. Volume I: *The Cortex of the Newborn*, Cambridge, Harvard University Press, 1939. Volume II: *The Cortex of the One-month Infant*. Idem, 1941.
5. MCGRAW, M. B.: *The Neuromuscular Maturation of the Human Infant*, New York, Columbia University Press, 1943.

Chapter II

RESPIRATION: FETAL ASPECTS

<i>Section 1</i>	. . .	Respiratory Activity Before Birth
<i>Section 2</i>	. . .	Fetal Activity in Relation to the Gas Content of Fetal Blood
<i>Section 3</i>	. . .	Oxygen and Carbon Dioxide Economy of the Human Fetus
<i>Section 4</i>	. . .	Respiratory Peculiarities of the Fetal Blood
<i>Section 5</i>	. . .	Clinical Summary

RESPIRATORY ACTIVITY BEFORE BIRTH

THE LIVING INFANT breathes at or very soon after birth, and in a manner not essentially differing from the respiration of the older organism. Measurements of the forces and volumes involved in the process may be made, their relation to metabolism explored, and the respiration of the neonatal infant thus presented in terms of its quantitative similarities to the adult. But what arouses speculation, investigation (and controversy), are such questions as:

1. What is the respiratory situation during intra-uterine existence?
2. What is the relationship of the intra-uterine respiratory state to that following the severance from maternal surroundings at birth?
3. Can intra-uterine respiratory activity be regarded as preparatory for extra-uterine breathing?

These questions are, of course, by no means merely of academic importance, since a knowledge of their answers is essential to the prevention of asphyxia in the newly born, to the therapy of asphyxial states, and to the management of those respiratory problems peculiar to the premature infant. Until we know why most babies breathe when they emerge from the uterus we shall scarcely be sure why some babies do not.

For the present purposes, it would be more satisfactory to recount only what has been learned through the observation of human fetal and neonatal life, were it not for the fact that most experiments have necessarily been performed upon animals. The results in different species have often been contradictory, and for

this reason inferences from animal experimentation may be applicable to human life only with some reservations. The respiratory act is, nevertheless, so fundamentally and immediately essential to existence that all careful animal studies must have at least some bearing on the human situation. Therefore, it seems allowable to consider observations upon animal and human subjects together rather than separately.

Do rhythmic muscular movements similar to those of respiration as we know it occur in the fetus *in utero*? Bonar, Blumenfeld, and Fenning¹ have presented a detailed history of this subject. As they point out, Vesalius noted fetal respiratory movements* after interruption of the umbilical cord circulation while Winslow (1781) observed them in dog and cat fetuses with supposedly intact cord and placental circulation.¹ Beclard,² writing in 1813, was able to refer to several authors who had investigated the phenomenon, while the account of his own studies is interesting in view of its similarity to descriptions of observations made a century or more later. Thus, he states: "Frequently, following laparotomy, I opened the uterus of gravid female animals. I ligatured the neck of the living fetus still enclosed within the amniotic sac. On dissecting the trachea and bronchi, I found them to be filled with a liquid similar to amniotic fluid.

"In order to dissipate my doubts, I injected ink into the amniotic sac of a dog fetus. After a few moments, I ligatured its neck—it still lived—and found black water in the trachea and bronchi. . . .

"On carefully opening the gravid uterus of a mammal, one can clearly see . . . through the amniotic fluid, the fetus making mechanical respiratory movements, as after birth, only more slowly. Each inspiration is accompanied by an opening of the mouth, a dilatation of the nares, and a heaving of the thoracic walls. The movements are repeated in uniform and regular intervals. They are similar in general to the respiratory movements—rare and deep—of infants born in a stage of apnea, such as is called asphyxia of the new born. . . .

"I fail to know whether, besides the undoubted mechanical phenomenon of respiration occurring in the fetus (particularly when the maternal circulation is impeded), there also exists some chemical process between the amniotic fluid and the blood flowing through the lungs. . . ."

* The term "Fetal respiratory movements" is used in this section as less cumbersome than "Rhythmic movements of the respiratory type" and "Fetal respiration-like movements," but it is intended to convey only the somewhat limited meaning of these more cautious phrases.

It is noteworthy that Beclard not only observed movements, he also tested their action upon amniotic fluid by the injection of dye, and he speculated as to the teleological significance of aspiration of this fluid into the respiratory tract. It is also worth mention that he qualified the "undoubted" in the last paragraph quoted above by adding the parenthesis about circulatory interruption. From his time until 1888 only an occasional confirmation or denial of the existence of fetal respiratory movements appeared, but after that date renewed interest was engendered by the observations and convictions of Ahlfeld, who for nearly twenty years defended the affirmative side in a spirited controversy upon the subject. His considered opinions and collected observations, including many convincing kymograph records taken from the abdomens of pregnant women, were published in 1905.³ These were indubitable proofs of a phenomenon the existence of which has since been substantiated directly or indirectly by numerous authors. For convenience a number of the major studies have been summarized in Table 1.

TABLE 1
STUDIES OF FETAL MOVEMENTS OF THE RESPIRATORY MUSCLES

Name	Date	Subject	Method and Remarks
Winslow ¹	1781	Dog, cat	Observation of fetuses through uterine wall.
Beclard ²	1813	Dog, cat, rabbit	Observation through uterine wall; presence of ink in trachea and bronchi after injection into amniotic sac.
Beclard ²	1813	Human	Amniotic fluid in trachea and bronchi at delivery.
Preyer ⁴	1885	Guinea pig	Observation through amniotic sac, in saline bath.
Weber ⁵	1888	Human	Tracings from maternal abdominal wall.
Ahlfeld ³	1888- 1905	Human	Observation and tambour tracings from maternal abdominal wall differentiating fetal respiratory from maternal pulse waves. Presence of amniotic fluid in respiratory passages of newborn.
K. Reifferscheid ⁶	1911	Human	Observations and tracings.
Wislocki ⁷	1922	Guinea pig	Aspiration of chemically identified amniotic fluid into fetal trachea and lungs, and direct observation.
Corey ⁸	1932	Rat	Observations to show that respiratory movement might occur <i>without</i> asphyxia but <i>always</i> occurred <i>with</i> asphyxia.

TABLE 1 (continued)

Name	Date	Subject	Method and Remarks
Klemperer ⁹	1933	Guinea pig	Observation <i>in amnio</i> . Inhalation of starch and dye added to amniotic fluid.
Snyder & Rosenfeld ¹⁰	1936-39	Human Rabbits, cats, Guinea pigs	Motion pictures of maternal abdominal wall. Preparation of post-mature animal fetuses, with observations, motion pictures, proof of aspiration of amniotic fluid, and studies of anesthetic drugs and gases, and of maternal oxygen and carbon dioxide levels, regarding effect on fetal respiration.
Bonar ⁴ Fenning ¹¹	1938	Human Rabbits, dogs, rats	Observation. Observation, motion pictures, oscillatocapacigraph measurements.
Ehrhardt ¹²	1939	Human, animal	Roentgenograms of fetal lungs after injection of thorotrast into amniotic fluid.
W. Reifferscheid & Schmiemann ¹³	1939	Human	"Umbrathor" injected into amniotic sac 24 hours before Caesarean, and shown by roentgenogram to be in lungs before and after delivery.
Barcroft, et al. ¹⁴	1936-39	Sheep, goats	Observation <i>in utero</i> and <i>in amnio</i> . Movements usually observed only early in gestation, and then perhaps not spontaneous. Definitely not spontaneous when observed late in fetal life.
Windle, et al. ¹⁵	1938-39	Cats Chickens, ducks	Observation <i>in utero</i> (maternal decerebration). Observations and tambour tracings on unhatched birds through shell membrane. Effect of gas tensions on respiration of unhatched birds.
Windle, Becker, Barth & Schultz ¹⁶	1939	Guinea pigs	Thorotrast injection into amniotic fluid. Respiratory activity only during artificially produced anoxemia or CO ₂ excess. Otherwise only questionable movements. Amniotic fluid inhaled only under pathologic conditions.

The fact of respiratory movement in fetal life has been satisfactorily established, but from it grow other and perhaps more important questions: Are such movements a normal, constant, physiological part of intra-uterine life, and is extra-uterine respiration simply their resumption after the interruption of birth? The latter idea has found considerable acceptance, offering as it does an at-

tractively simple account of the onset of neonatal respiration. But one can hardly dismiss the evidence that such movements are not constantly observable on the abdominal surface of all women in late pregnancy, that they do not appear in every animal fetus directly observed *in utero*, and that some observers (Runge¹⁷, Schmitt¹⁸, Dyroff¹⁹ have been unable to see them at all. Undoubtedly such failures may sometimes have resulted from the use of maternal anesthesia, for Rosenfeld and Snyder,^{10,c} have demonstrated the significant cessation of fetal movements when various sedatives and anesthetics are administered to the maternal animal. Even so, Ahlfeld himself freely admitted that the movements he registered from the abdominal walls of non-anesthetized pregnant women were not continuous. "Sometimes," he said, "they lasted an hour,"³ and this implication of an expected cessation is an extremely important argument against the idea that any constant "respiratory" activity of the human fetus is simply resumed post-natally. Those who work with animals having large litters have always noted the tendency for some fetuses in any uterus to be quiescent while others display active thoracic movements. In the wide experience of Snyder and Rosenfeld, the number in any litter of rabbit fetuses showing these movements at any given time was not all of those observed.¹⁶ Bonar, Blumenfeld, and Fenning¹ comment on the same chronological and individual inconstancy of the phenomenon in animals observed, and Klemperer⁹ noted no respiratory movements in 27 per cent of the fetal animals he studied.

If such movements are to be understood as essential preparations or precursors for extra-uterine respiration in human and animal fetuses, this irregularity in their appearance is accounted for with difficulty; its interpretation requires data as to the place of the whole phenomenon in relationship to fetal life and activity. If fetal respiratory movements are not constant physiologic manifestations, under what stimuli are they called forth, and under what conditions are they in abeyance?

Here, in the understandable absence of a series of chronological observations upon the human fetus *in utero*, one is grateful for the painstaking work of Barcroft and his colleagues on the development of fetal respiratory activity in the sheep. In numerous highly readable papers and particularly in the first chapter of *The Brain and Its Environment*^{14,c}, these workers have described the events occurring in the fetus of this animal from about the 34th day (when the organism is no larger than the human thumb-nail) to birth at about 147 days. At 34 days, stimulation of the maxillary branch of

the trigeminal nerve (tapping the fetal face just below the eye) leads to a jerking of the head which is the earliest fetal movement. By a gradual progression from one more or less definable stage to another as gestation advances through the next few days, the extent of this response spreads to include the thoracic muscles and diaphragm. It assumes a prolonged, rhythmical, and respiratory nature, and its presence is called forth by weaker and much more diffuse stimuli. "By the end of the seventh week it is almost impossible to hold the fetus so quietly as to avoid liminal stimuli producing respiratory movement."^{14, b} However, one thing which does *not* act as a stimulus producing such movement at this gestational stage is the asphyxial effect of clamping the umbilical cord.

After the 7th week an increasingly quiescent state supervenes in which stimuli elicit little movement unless the fetal central nervous system be transected at the midforebrain, or exposure of the fetus be allowed, or *asphyxia be now produced by clamping the cord*. The fetus, according to Barcroft, has at this age progressed into a state of inhibition, wherein alteration from quiescence to activity involves some sort of release. So the organism continues through the rest (and the major portion) of its gestation, making no spontaneous intra-uterine respiratory movements unless its cord circulation be disturbed. Thus, it appears that the fetus of the sheep, at least, displays an early stage of respiratory activity not dependent upon chemical stimulus, followed by a prolonged period during which chemical and perhaps tactile stimuli are the keys which release the respiratory response. We cannot consider respiratory movements as an automatic, constant, or progressive activity of these animal fetuses but rather as a response pattern, acquired early and held in abeyance for use under certain conditions much later. Barcroft and Barron^{14, b} state, "When first seen, the movements seem to depend upon some as yet ill-understood stimulation of the fetus." To answer their own question as to whether the fetus at this early stage would make "rhythmic movements of the respiratory type" if not interfered with (i.e., stimulated) at all, they tried to observe the transilluminated fetus *in utero*. While rhythmic movements were observed, the authors were not convinced that all manipulation had been entirely avoided.

Other fetal animals have their chronological stages during which they are "apneic." Windle, Monnier, and Steele^{15, b} have shown this to occur during mid-gestation in the cat although at this time, as with the sheep during its later two-thirds of intra-uterine existence, interference with circulation by pinching the cord will call forth thoracic movements. Windle, Becker, Barth, and Schultz¹⁶ have

recently brought forward evidence which suggests that "rhythmical movements of a respiratory nature" do not occur in the more mature guinea pig fetus unless under the stimulus of interference with maternal respiration. Such observations suggest to them that respiratory movement is not to be considered a constant fetal activity. Certainly the gestational period when it is most in evidence is not the same for all species.

Unfortunately, we have little data as to the chronology of fetal respiratory activity in other experimental animals, and none at all as regards man. Most observers of human subjects have stated that the respiratory rhythms occasionally noticeable through the maternal abdominal wall are a feature of the latter part of pregnancy,³ although Reifferscheid and Schmiemann¹³ noted that radio-opaque material introduced into the amniotic sac at five months gestation was aspirated to a degree which was roentgenologically observable in the fetal lungs after premature delivery. Windle, Dragstedt, and others²⁰ have observed respiratory movement in a twelve-week human fetus when the placental interchange was interrupted; Mahon²¹ saw a spontaneous movement of the fetal arm and thorax upon opening the uterus of a woman eleven weeks pregnant; and Fitzgerald and Windle²² have recently reported trunk, arm and leg movements in human fetuses of only 54 to 58 days gestation, carefully preserved from anoxia and narcosis. Thus, as with the fetal sheep, the observations upon human subjects show at least a potentiality for muscular and thus respiratory activity over a long span of fetal life. A chronological study of such movements throughout developmental life is needed before one can prove or disprove other similarities between the various mammalian species.

FETAL ACTIVITY IN RELATION TO THE GAS CONTENT OF FETAL BLOOD

Since respiratory movement seems to be of an occasional, inconstant nature during fetal life, its almost unfailing appearance after birth can hardly be thought of as the direct continuation of a regular intra-uterine activity. If, on the other hand, it can be shown that respiratory movement is regularly called forth in late fetal life by an asphyxial stimulus, then the first breath after delivery must obviously be the result of an asphyxial mechanism, brought about as it would be with absolute completeness and finality by the birth process. This simple explanation is not in agreement with the reports of every worker, although most observers from the time of Vesalius have noted fetal respiratory efforts as a result of circu-

latory interruption experimentally produced, and Runge,¹⁷ Cohnstein and Zuntz,²³ Schmitt,¹⁸ Dyroff,¹⁹ and others, have taken the stand that no respiratory movements whatever occur in the fetus, except in response to such asphyxial situations. The problem could best be solved in terms of chemical measurements, but the critical levels of oxygen deficiency or carbon dioxide excess at which respiratory activity is released in the human organism at or before birth are not known. However, most samples of cord blood taken for investigation have been secured at normal birth and their gas concentrations may be somewhere near those usual at respiratory onset.

Before presenting such chemical data as are available from human births a chronological description of blood oxygenation during the course of fetal life in another species may be worth stating. This has been furnished from studies on the sheep by Barcroft, Kennedy, and Mason.²⁴ Their analyses have shown that the amounts of oxygen reaching the fetus in the umbilical vein and leaving it in the umbilical arteries are not constant quantities throughout intra-uterine life. The "oxygen environment" of the fetus displays a fairly regular rise to the 90th or 100th day of gestation, at which time the blood reaching the fetus in the umbilical vein may attain an oxygen saturation of 90 per cent or more. From then until near normal birth (about the 145th day) there is a gradual falling off to 70 or 80 per cent saturation, and a more abrupt drop in the final week to 60 or 70 per cent. The blood leaving the fetus in the umbilical arteries shows a somewhat parallel performance, with the significant exception that its oxygen content tends to approach rather more closely that of the umbilical vein as term nears. The resultant effect must be that towards delivery the fetus retains considerably less of the oxygen brought to it from any given quantity of umbilical vein blood than was the case earlier in pregnancy.

A highly important conclusion from this work is that earlier publications of single measurements of the fetal blood oxygen concentration may not be accepted as representing the situation throughout gestation, since the figures just presented follow a waxing and waning curve. In the sheep, at least (and it is logical to suppose something of the same sort occurs in other mammals as well), what holds true for the oxygen supply at term would not apply to mid-pregnancy. A further significant observation made by these authors²⁴ was that samples taken from the umbilical vessels varied as to oxygen content inversely with the degree of manipulation of the uterus and cord at the time of sampling. The more carefully and rapidly specimens were taken, the less variable *and the*

more elevated were their oxygen contents. Altogether it appears that work heretofore considered as proving normal fetal existence at low oxygen tensions may have to be accepted with some reservations. The fetus during much of intra-uterine life may not be nearly so anoxicemic or so cyanotic as has been believed the case, and even during labor itself the true fetal oxygen supply may be somewhat better than many of the experimental data have indicated.

Some quantitative measurements of the oxygenation of blood reaching the fetal brain during late gestation have been published recently from Barcroft's laboratory.²⁵ Again, there was evidence that the figures normally rose and fell during the fetal career, as did the levels of artificially produced anoxemia sufficient to bring about thoracic movement. The older the fetus, the greater the degree of cerebral anoxia which could be tolerated before the critical level of respiratory onset was reached; moreover, toward the end of pregnancy, the oxygenation of carotid blood in the normal quiescent fetus fell constantly *toward* this critical level, "so that by the 146th day the actual conditions under which the fetus lives are very close indeed to those at which respiratory release takes place, whilst at the earliest stages a very ample margin exists."

This study is strong evidence that at birth the sheep breathes as a response to a chemical stimulus and not merely as a continuation or resumption of an established activity. Obviously, only one chemical factor has been measured. The facts regarding the carbon dioxide tension, that much more efficient respiratory stimulus of ordinary extra-uterine life, are not available from these data. These are, however, the only longitudinal chemical studies at present available, and they reiterate the importance of circulatory interruption in releasing respiratory activity at and before delivery.

An early experiment performed by Cohnstein and Zuntz,²⁶ although furnishing no chemical data, is worth recounting here. Since those authors found it almost impossible to open the uterus of a rabbit or guinea pig without significantly altering the placental circulation, they also used the sheep. A fetus was partially removed from the uterus, so that the nose and front quarters were in the air. (No mention is made of anesthesia.) Tickling and otherwise stimulating the skin and mucous membranes of the fetal face caused no respiratory activity whatever. Even when the fetus was removed entirely into the air (care being taken to keep the cord undisturbed), it still did not breathe although it made some movements of the limbs and sucked upon a finger placed in its mouth. Moreover, it was not cyanotic. Almost immediately upon the cord being tied, the fetus breathed. This experiment not only shows the

ineffectiveness of sensory stimuli, it also substantiates the observations of the Cambridge physiologists upon the critical importance of circulatory interruption for respiratory onset.

The implications from work upon the sheep seem very simple and clear but other authors have been led to quite different conclusions regarding the chemical regulation of respiratory movements in smaller animals. Snyder and Rosenfeld^{10, b} observed the activity of rabbit fetuses in the unopened uterus (at or after normal term),* during procedures calculated to alter the gas relationships of the maternal blood. It was logically assumed that the fetal blood would be correspondingly altered, although no chemical measurements could be made. During the control periods, the fetuses were either making the rhythmic respiratory movements described by these authors as so constant in small animals or they were for the moment quiescent. The experiments resulted as follows: Anoxemia always stimulated the maternal respiration but invariably depressed that of the fetus. Those fetuses which happened to be quiescent were *never* stimulated to respiratory activity by maternal anoxemia. Increase in carbon dioxide increased maternal respiration but produced no effect upon the respiratory state in two-thirds of the fetuses. In the other third there was stimulation of respiration. Carbon dioxide deficit resulted in maternal and fetal apnea. The authors conclude that a certain minimal CO_2 tension must be required for fetal respiratory movement. Although technical difficulties make it hard to obtain samples from the vessels of such small fetuses, and the resulting measurements may not be quite reliable as representing the actual situation in the animal, Snyder recently published some very suggestive data from specimens of umbilical cord blood. These demonstrated "a striking decrease in the oxygenation of fetal blood during induced apnea, the oxygen saturation often falling to one-third of that observed before and after induction of apnea." The apnea was brought about in these rabbits by the administration of a low oxygen mixture to the mother animal, who responded with respiratory stimulation.²⁷ It is possible to conclude that the rabbit fetus at term is not responsive to anoxemia nor usually to excess of CO_2 . Under such circumstances one must assume that clamping or cutting the umbilical cord might tend only to depress the respiratory activity of the newborn animal. This is of course quite at variance with the work of Barcroft's group described above.

* Animals were carried past normal gestation by administration of anterior pituitary-like substance to the mother.

Windle, Monnier, and Steele^{15, b} have shown that the cat seems to have its fetal differences from both the sheep and the rabbit as regards chemical regulation of respiratory activity. Observations of the fetuses while various respiratory mixtures were supplied to maternal cats indicated to these authors that whereas an excess of maternal CO₂ was not a respiratory stimulant to the fetus near term, conditions tending to *increase* fetal oxygen supply did bring about "respiratory rhythms." The interpretation was offered that the cat fetus at or near term is depressed and in a state of partial anoxia, and that conditions tending to alleviate this anoxia thus result in respiratory activity. But how this is to be related to the onset of breathing following the complete anoxia necessitated by birth is not explained, except as the authors bring forward their observation of the effectiveness of uterine contractions in bringing about increased redness (i.e. oxygenation) of the umbilical vein blood, as though the contracting uterus were pumping oxygen to the fetus while it descends the birth canal. Thus, although birth itself may terminate with complete anoxia for the fetus, the birth process may be one offering extra oxygen until this termination.

The problem remains one at present in which much labor and ingenuity have been expended without the derivation of any universal principles governing fetal—or neonatal—respiration. The idea has been advanced by Barcroft^{14, c} that fetal animals in which movements of the respiratory muscles are observed to cease during induced anoxia, may have been (despite technical precautions) somewhat asphyxiated in the first place, and that the experimental stimulus is thus not being applied to a normal organism. An absolutely normal fetus *in utero* may then undergo no movements of the respiratory muscles except under the influence of some stimulus, asphyxial or otherwise. A slightly asphyxiated fetus, responding with respiratory movements, might well cease to make such movements under the disturbing influence of further (experimentally induced) asphyxia—whether essentially the result of a diminution of oxygen, an excess of carbon dioxide, or both.*

It may be that to expect a single inference to emerge from studies on the rabbit, guinea pig, cat, and sheep, whose gestation periods spread from 32 to 145 days—and to anticipate that such an

* Barcroft and Young⁵⁹ have recently compared rabbit fetuses carried past normal gestation and those at and before normal term, with regard to blood oxygenation. A progressive deterioration in oxygen saturation of blood from the fetal brain was demonstrable during the period of post-maturity. Conclusions drawn from post-mature fetuses may thus be inapplicable to normal fetuses.

inference might be applicable to human fetuses with their 280 days of gestation—is, after all, perhaps unwarranted. Were it possible for all work to be done on the same species—or, perhaps better still, for authorities to trade experimental animals—progress toward understanding might be accelerated.

OXYGEN AND CARBON DIOXIDE ECONOMY OF THE HUMAN FETUS

One returns to the human fetal and neonatal situation with considerable misgiving, since the foregoing recital of animal observations may have resulted only in complete confusion. Actually, the human subject is almost entirely unexplored by contrast to what is known of certain other species. But as an essential postulate it may be said that constant fetal respiratory activity has certainly not been proven and is almost certainly not present in man. Although the bulk of work on the human subject has been in the form of chemical measurements, we have no very satisfactory data as to the oxygen and carbon dioxide levels to which the human organism is acclimated during its later intra-uterine existence. Such data would be worth having, since departure from usual gas concentrations probably stimulates such human fetal respiratory movements as have been observed, and could thus explain the onset of extra-uterine breathing at birth. Eastman²⁸ has indeed examined the contents of a loop of cord withdrawn before the delivery of an infant at elective Caesarean section under local anesthesia, and obtained oxygen measurements of 13.3 and 6.3 volumes per cent in blood from the umbilical vein and arteries respectively. These are amounts considerably below the 19 and 15 volumes per cent of normal adult life. These data would be very illuminating and useful for understanding fetal conditions, were they substantiated. Haselhorst and Stromberger,²⁹ however, sampled the cord vessels at eight elective Caesarean operations performed before labor and obtained averages of only 3.5 and 0.9 volumes per cent in vein and arteries—figures far below those found by Eastman. Of course the samples may not have been obtained in exactly the same way. At other Caesarean deliveries after several hours of labor, Haselhorst and Stromberger found average oxygen values of 12.0 and 2.8 volumes per cent for the umbilical vein and arteries; these were still not so high as Eastman's observation but were sharply elevated above the values just mentioned for fetuses removed from the quiescent uterus. This improvement over the situation before labor the authors attributed to improved placental blood supply

resulting from uterine contractions. The agreement of this observation with that of Windle and his colleagues^{15, b} upon the cat fetus is notable and refreshing in a field so troubled with conflicting evidence.

To show something of the amount and scope of chemical investigations, most of the figures from the literature on oxygen and carbon dioxide levels in human and animal fetal blood have been enumerated in Tables 2 and 3. Rather wide variations, particularly as regards oxygen in the umbilical vein, are apparent. Were the individual results rather than the averages from various authors given, the scatter of findings would be still more striking. This need not imply that the figures are untrustworthy but is merely evidence as to the numerous and varied factors affecting the oxygen and carbon dioxide economy of the fetus *in utero* and of the newborn at delivery. Perhaps the wonder is that in any given species the fetus is able to show as relatively constant a balance as is present before it can get free of the maternal surroundings and regulate its blood gases by its own respiration.

Keeping in mind the observation of Barcroft and others²⁴ that the oxygen levels are depressed by handling or manipulating the cord, a few remarks may be made concerning these data:

1. The blood arriving at the fetus from the placenta at the onset of extra-uterine respiration has usually been found to be saturated to only about 50 per cent of its oxygen capacity. The capacity varies with the species, but in man is about 20 volumes per cent, so that to the human fetus each 100 cc. of blood is carrying some 10 cc. of oxygen (10 vols. per cent).

2. That leaving by the umbilical arteries to return to the placenta carries only 2 or 3 volumes per cent, so that about 7 cc. of oxygen are deposited in the fetus by every 100 cc. of blood arriving from the placenta. The arterio-venous difference in human adult blood is not nearly so great as in human fetal blood, a comparison which suggests that the oxygen of fetal blood, although available at low tensions, is rather well utilized. Without definite knowledge of fetal circulation time, or numerical data as to the intermingling of streams in the fetal circulation, this remains inference rather than fact.

3. In general, severe grades of neonatal apnea or asphyxia are accompanied by low levels of oxygenation, an observation also made by Wilson, Torrey and Johnson,⁴⁴ whose data are not tabulated.

4. Maternal anoxemia is reflected by anoxemia in the fetus.

TABLES 2 AND 3
RESPIRATORY GASES IN BLOOD OF ANIMAL AND HUMAN SUBJECTS, AT AND BEFORE BIRTH
2. OXYGEN (In volumes per cent unless otherwise stated)

<i>No. and Author</i>	<i>Date</i>	<i>Subject</i>	<i>Maternal:</i> Arterial Venous Content Content		<i>Vein</i> Content	<i>Umbilical:</i> (% Sat.)	<i>Artery</i> Content	<i>Capacity</i>	<i>Remarks</i>
1. Cohnstein & Zuntz ²⁰	1884	Sheep			6.3	(42.3)		14.9	Apparently before birth
2. Huggett ²¹	1927	Goat			8.0	(43.6)	2.9		Averages, 6 fetuses, at or before term
3. Kellogg ²²	1930	Dog	13.0	9.4	2.9 to 10.1	(11 to 60)			Fetuses at term
4. Roos & Romijn ²³	1938	Cow	12.4	8.9	9.8	(90)	4.9	11.3	O ₂ in fetal blood rises to 90% just before term
5. Barcroft, Flexner, McClurkin ²⁴	1934	Goat			3.9 to 8.5	(33 to 81)			Last half of pregnancy
6. Barcroft, Kennedy, Mason ²⁴	1940	Sheep			10.1 11.4 10.3	(93) (98) (75)	3.4 4.7 6.6		Mid-pregnancy—3 fetuses
					10.6 12.8 8.6 12.3 8.5	(50) (70) (48) (65) (65)	4.3 6.2 4.8 4.8 5.3		Near term—5 fetuses
7. Steele & Windle ²⁵	1939	Cat	15.7 12.3	8.9 7.4	2.1 6.5	(15) (46)		14.2	Mid-pregnancy
									Near term
									Ave. 22 apneic fetuses
									Ave. 13 active fetuses
8. Eastman ²⁵ & ²⁵	1930	Human	14.9	10.8	13.3	(64)	6.3	20.9	Elective Caesarean.
		Human	14.7	11.0	10.5	(50)	3.3	20.8	At normal delivery
		Human		10.2	1.3				6 asphyxiated infants
9. Haselhorst & Stromberger ^{26, 27}	1930	Human			10.1	(45)	3.4	22.2	Ave. 32 at birth
	1930	Human		10.3	12.0	(54)	2.8		Caes. after labor (Ave.)
	1932	Human	14.4	9.9	3.5	(16)	0.9		Caes. before labor (Ave.)
10. Noguchi ²⁷	1936	Human		9.0	10.2	(48)	3.4	21.4	30 at birth.
11. Bidone ²⁸	1931	Human		11.6	14.9		12.6		9 during physiol. apnea
12. Goldbloom & Gottlieb ²⁹	1930	Human		17.5	17.2	(80)		21.5	Ave. of 9 normal births, computed from authors' data
13. Smith ³⁰	1939	Human	16.2	15.3	12.0	(57)	3.3	21.3	21 other deliveries
		Human	12.8	11.5	7.0	(33)	2.1	21.5	21 N/O deliveries

TABLES 2 AND 3—Continued
3. CARBON DIOXIDE (In volumes per cent unless otherwise stated)

No. and Author	Date	Subject	Maternal: Arterial Venous Content Content	Vein Content	Umbilical: Artery Content	Remarks
1. Cohnstein & Zuntz ²⁰	1884	Sheep	46.5	43.1	45.1	Only few animals, before birth
2. Huggetti ²¹	1927	Goat	—	29.9	41.5	Ave. of 6 goats, near or at term before labor
3. Keys ²¹	1934	Goat	—	29.9	41.5	Ave. of 2 animals
4. Kellogg ²²	1930	Dog	35.6	33.1 to 46.3		Fetuses examined under local or spinal anesthesia at term
5. Roos & Romijn ²³	1938	Cow	34.8	52.7	58.5	
6. Steele & Windle ^{15, 24}	1939	Cat	27.8 25.3	36.7 46.6		Mid-pregnancy Near term Ave. apneic unborn fetuses Ave. active unborn fetuses
7. Rielander ²⁵	1907	Human		24.2 to 47.0		Series of 17 infants at birth
8. Kane & Krieselman ²⁶	1930	Human			Mixed Vein and Artery 54.6 47.3 44.9	Ave. 7 asphyx. infants Ave. 26 gasping infants Ave. 14 crying infants
9. Eastman ²⁴	1932	Human	43.3 31.2 37.5 37.6 42.6	45.9 (35.5 mm.Hg.) 35.5 (61.6 mm.Hg.)	51.2 (41.3 mm.Hg.) 37.3	Ave. 8 normal infants at birth (CO ₂ tension) 6 asphyxiated infants at birth (CO ₂ tension)
10. Haselhorst & Stromberger ^{25, 26}	1930 1932 1930	Human Human Human	39.2 42.7 30.6	40.7 44.8 35.5	46.2 46.8 44.6	Ave. 32 normal at birth Ave. 8 Caesarean before labor Ave. 2 Caesarean after labor
11. Bidone ²³	1931	Human	49.3	41.2	50.1	Ave. 9 at normal birth
12. Noguchi ²⁷	1936	Human	37.0	39.1	46.7	Ave. 30 at normal birth

5. The carbon dioxide figures, mostly the expression of amounts rather than tensions of gas present, also show variations. With certain exceptions⁴⁵ omitted from the table, the amounts of carbon dioxide in fetal blood *in utero* and at birth are usually slightly higher than in the mother's circulation.*

6. Where *tensions* of CO₂ at birth have been determined they tend (because of somewhat increased hydrogen ion concentration in fetal blood) during and after delivery to be well above the maternal tension. In asphyxiated infants Eastman³⁵ has shown the carbon dioxide tension to be particularly elevated.

In our own laboratory we have come to similar conclusions, namely that in human infants slow to breathe at birth the carbon dioxide tension tends to be excessive rather than reduced, while the oxygen supply is reduced rather than in excess. Infants breathing promptly at birth may show, however, widely scattered CO₂ tensions. In a study of the carbon dioxide dissociation curves of fetal blood, Eastman and his colleagues⁴⁶ have presented data as to the tension of this gas at the exact moment of respiratory onset in seven normal infants. A carbon dioxide tension of 45–50 mm. Hg is supposedly an adequate stimulus to respiration, whereas the values obtained by Eastman were distributed from 38 to 65 mm. or, as he says, "throughout the entire physiological range." He was "unable to establish any optimal range of carbon dioxide tension particularly favorable for the onset of respiration, . . . a circumstance which suggests that some factor other than the carbon dioxide tension of the fetal blood is the dominant one in initiating this phenomenon."

RESPIRATORY PECULIARITIES OF THE FETAL BLOOD

Although they have no direct bearing on the cause of respiratory onset at birth, studies on oxygen and carbon dioxide dissociation curves may here be discussed since consideration of the relationship between fetus and mother across the placenta requires information as to whether the respective bloods are strictly comparable in terms of the way they take up and release the respiratory gases. Moreover, consideration of the newborn infant as a breathing organism requires knowledge of any peculiarities in the respiratory function of its blood which may carry over from the fetal state.

As will be seen from the carbon dioxide dissociation curve of human fetal blood at birth, published by Eastman, Geiling and

* This can not be taken as evidence of a greater alkali reserve in the fetus, even though Keys⁴¹ found evidence to support such a possibility in blood from goat fetuses.

DeLawder,⁴⁶ "at all gas tensions the fetal blood releases carbon-dioxide more readily than does the blood of the mother." For example, it will be noted from the curves that at 50 mm. Hg tension of carbon-dioxide ($p\text{CO}_2$) the fetal blood can not retain more than about 40 volumes per cent CO_2 , while the maternal blood, with its curve lying to the left and above that for the fetus, will retain

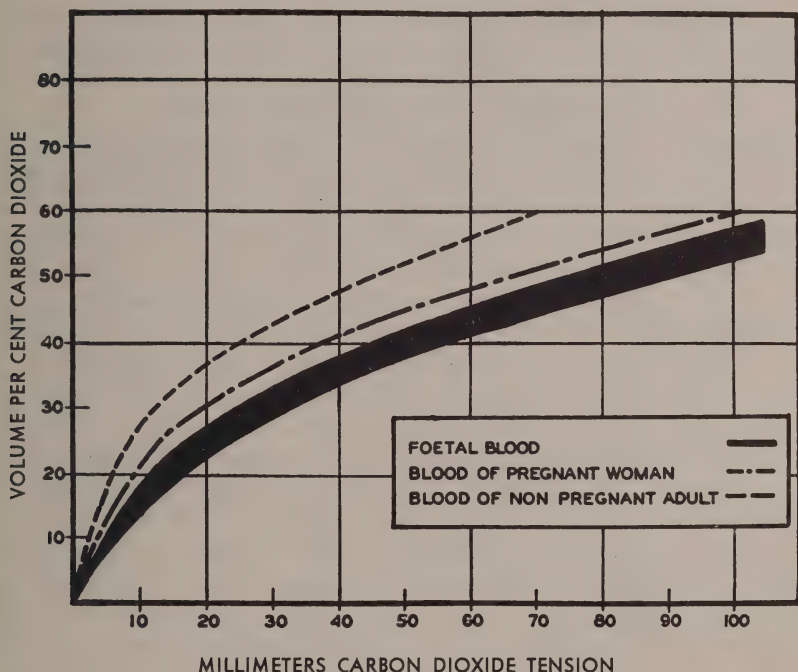


FIGURE 1

The carbon dioxide dissociation curve of fetal (umbilical vein) blood; showing the range encountered in the bloods from five infants as compared with that from the pregnant woman and from the normal non-pregnant adult. At any tension the maternal blood appears able to become more saturated with carbon dioxide than the fetal. (Eastman, Geiling, DeLawder, *Bull. Johns Hopkins Hospital*, 53: 246, 1933.)

45 or more volumes per cent at this tension. Obviously, tensions at which fetal blood must give off carbon dioxide will therefore be compatible with its acceptance by maternal blood. This ingenious arrangement of nature probably results from the excess hemoglobin of fetal blood at term, from its decreased total base, and perhaps from other differences between it and the blood of the mother. A study by Keys⁴¹ in which the CO_2 dissociation curves of

fetal goats were found to be above rather than below those of the maternal bloods, was based upon pregnancies only two-thirds or three-quarters of the way to term. The amount of fetal hemoglobin was then lower and the alkali reserve higher than in the maternal organism. Observations of these relationships in the human mother and fetus a few months before term would be of interest, but there is no reason to suppose that when the human infant is born its blood behaves otherwise with respect to carbon dioxide than is shown in Eastman's diagram. Nor does the work regarding carbon dioxide give any suggestion of differences other than quantitative between the blood of the fetus and the adult.

The matter of oxygen transport has been approached as one of several aspects in which the hemoglobin of fetal blood might differ qualitatively as well as quantitatively from that of the mother. Much use has been made of experimental animals, so that observations are available on the blood of chicks, rabbits, calves, sheep and goats; from most of this work has come information at least suggesting that fetal hemoglobin is actually a qualitatively different substance from that of adults. Roos⁴⁷ mentions reported differences in affinity for oxygen, in resistance to alkali denaturation, in spreading velocity, and perhaps in the shape of crystals. Immunological study of human umbilical cord blood and human adult blood has shown precipitin reactions indicating that the blood at birth contains two immunologically different hemoglobins.⁴⁸ Although Haurowitz⁴⁹ also mentions identification of human fetal hemoglobin by spectrophotometric measurement, Jongbloed⁵⁰ was able to show an exact similarity between the spectroscopic absorption curves of hemoglobin from five newborn infants and their mothers. The reader is referred to Roos⁴⁷ and to Windle⁵¹ for reviews of a subject upon which the final word has certainly not been spoken.

The oxygen affinity of fetal hemoglobin is most easily considered in terms of its dissociation curve, which may be conveniently compared to that of the mother's blood. An example of what striking changes have been found to occur at certain stages of fetal life is shown in the accompanying figure. Here the curve for fetal blood in the goat at about nine-tenths of total gestation lies much to the left of the normal range, while the maternal curve has shifted toward the opposite direction. As a result, it will be observed that at some 30 mm. of oxygen tension (abscissae) the fetal blood can become 60 per cent saturated with oxygen, while the maternal must relinquish all but about 30 per cent of the oxygen it can carry. Bar-

croft,⁵² from whose work this illustration is taken, has shown how not only the positions, but the shapes of the two curves favor transport of oxygen to the fetus during pregnancy, and how, by the time the kid is born the fetal curve has "worked over" to about the normal shape and position for the adult animal, although the maternal curve is still advantageously (for the fetus) to the right of normal. This is about where Eastman, Geiling, and DeLawder⁴⁶ found the two curves in human infants and their mothers at birth. Haselhorst and Strom-verger⁵³ actually found the neonatal human curve to the left of the normal, as with the fetal animal. On the other hand, Noguchi,⁵⁴ who takes exception to the technique used by Haselhorst and Stromberger, could discover no differences between the oxygen dissociation curves of neonatal and maternal human bloods.

Darling, Smith, Asmussen and Cohen⁵⁵ have found the curves for all of ten human fetuses (including two at five and seven months gestation) to be regularly to the left of the normal adult position while the maternal curves moved gradually to the right as pregnancy advanced. The maternal curves somewhat overlapped the normal range, but all of the fetal values lay to the left of it (Fig. 3). The data were obtained at constant pH, rather than constant $p\text{CO}_2$ as in the work of other investigators, since there is reason to believe the values at constant pH give more useful evidence as to possible differences in hemoglobin. A feature of particular interest was the similarity of the

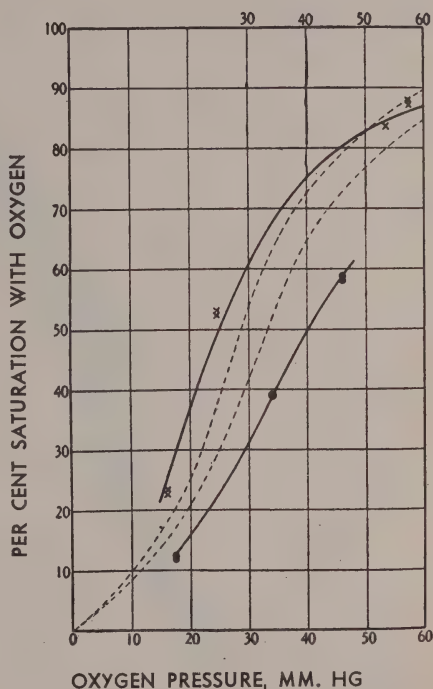


FIGURE 2

Oxygen dissociation curves of the goat fetus (left), and its mother (right), at near term. Broken lines outline range of curves from non-pregnant adult goats. Note that the maternal-fetal oxygen relationships are the reverse of those for carbon dioxide. (Barcroft, et al., *J. Physiol.*, 83: 192, 1934.)

curves for the young fetuses in position and shape to those for full-term infants; the human fetus at five months appeared to be no better off in regard to this mechanism for oxygen uptake than the fetus at term, in contrast to the animal fetuses examined by Barcroft.

A second point of interest was the observation that five days after birth the oxygen dissociation curve of the infant's blood lay

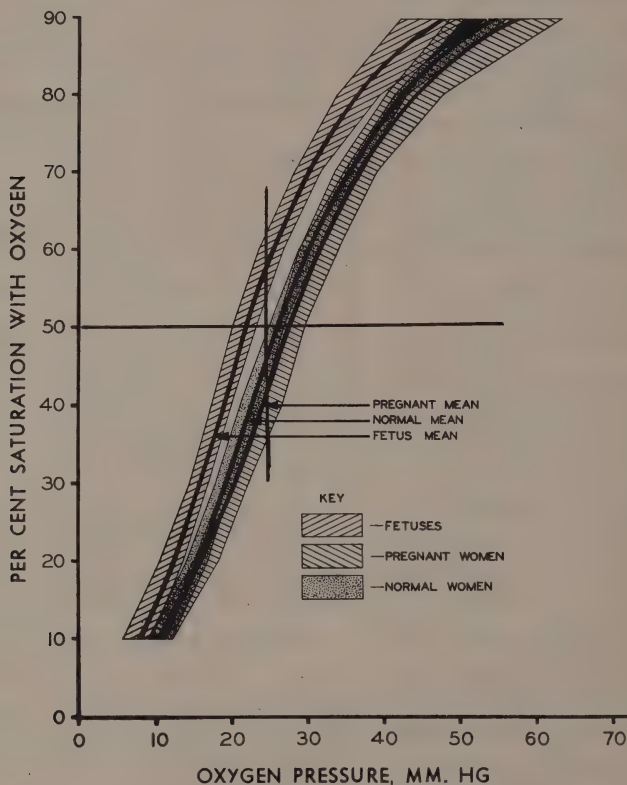


FIGURE 3

Oxygen dissociation curves of human infants at birth, pregnant women, and normal non-pregnant women. Means indicated by black lines, ranges by shading. Compare with Figure 2. To orient the data of Figure 4, axes have been drawn at 50% O_2 saturation (horizontal) and 25 mm. Hg O_2 tension (vertical). (Darling, Smith, Asmussen, Cohen, *J. Clin. Investigation*, 20: 739, 1941.)

to the left of the normal, and in one infant the curve was still in that position at one month of age (Fig. 4). By this time the infant should be biochemically like an adult individual, and any persistence of the fetal dissociation curve would suggest persistence of a fetal hemoglobin. Those who have spectroscopically or by other

means identified what they believe to be fetal hemoglobin in newborn animals and human infants give varying accounts of its persistence in the blood after birth. In most animal studies a diminishing proportion of the substance remains for a few days or weeks in the young animals' blood, and this is probably true of differences between the blood in the human fetus and infant. Jonxis⁵⁶ claims

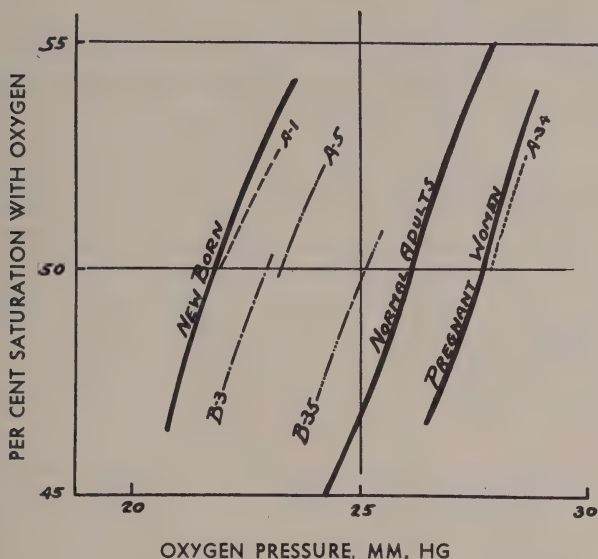


FIGURE 4

Positions of oxygen dissociation curves in two infants at varying ages after birth. Axes, and curves for newborn infants, normal adults, and pregnant women, as in Figure 3.

A-1, A-5, and A-34 indicate curves for blood of Baby A on 1st, 5th, and 34th day; B-3 and B-35, blood of Baby B on 3rd and 35th day. It will be noted that the neonatal curves require several days to reach the adult average, and that one moves somewhat beyond it.

that a fetal type of hemoglobin persists in the blood of prematurely born infants until the expected day of birth and only then begins to disappear. Such a phenomenon would not greatly alter the relationship of the newborn infant to his environment during the beginnings of extra-uterine life, although the presence of hemoglobin having an increased affinity for oxygen might, of course, be of assistance in states of inefficient pulmonary function. Conversely, it must be remembered that an unusual avidity of hemoglobin for oxygen would interfere with the release of that gas from the capil-

larities to the fetal and neonatal tissues. This consideration is, at least in fetal life, of rather minor significance since at that time the tissues appear to use comparatively low amounts of oxygen (see p. 140).

The intriguing question of an actual qualitatively unique fetal form of hemoglobin in man is still not settled by the oxygen dissociation observations reviewed above, since the increased affinity of fetal blood for oxygen could be the result of difference in permeability of fetal red cell membranes as compared with the walls of maternal cells. "If the cell membrane of the fetal red cell has the same characteristics of permeability as that of the adult cell, then the fetal hemoglobin has truly different properties."⁵⁵

Fetal and neonatal blood has two other characteristics of considerable respiratory significance. One is the augmentation of red blood cells and hemoglobin which is well known to exist through this general period, and must tend to increase the amount of circulating oxygen. The other, to which Stevenson recently called attention,⁵⁷ may have an unfavorable effect upon the respiratory function of the blood. This is a deficiency in carbonic anhydrase, an enzyme which accelerates the reaction



and, by favoring a prompt release of carbon dioxide in the lungs, makes for rapidity and flexibility in the uptake of oxygen there. Although present in adult blood in a considerable excess over emergency needs, carbonic anhydrase tends to be low in the blood of fetal animals,⁵⁸ premature infants, and full term infants. Stevenson's data show concentrations, in arbitrary units, of 0.79 for the enzyme in the blood of premature infants, 1.41 for full-term infants, and 3.51 for adults. Since the same author has proven that transfusion with adult blood definitely increases the carbonic anhydrase activity in premature infants, and since a general clinical improvement is then also notable, it appears probable that carbonic anhydrase may be of more than academic importance in neonatal physiology.

CLINICAL SUMMARY

It seems probable that the human fetus receives an oxygen supply which, although less than that serving the tissues in extra-uterine life, is insufficient to induce constant movements of the respiratory muscles *in utero*. On the other hand, such movements may normally occur following occasional stimuli from transient interference with the maternal, placental, or umbilical mechanisms

for oxygen provision. The ability of the fetus to respond in this manner is, indeed, the best guarantee that the infant will be able to assume its respiratory responsibilities at birth, for it is most probable that extra-uterine respiration is begun as a response to anoxemia, with or without excess of carbonic acid. The subject will be further discussed in the next chapter.

Intra-uterine life is accompanied by a proportionately excessive amount of available hemoglobin, and by a qualitative individuality of hemoglobin which is probably a fundamental characteristic of fetal existence. Both of these factors persist, in declining degree, into the first few weeks of extra-uterine life. The former allows more oxygen to be carried per unit of neonatal blood; the latter favors a more avid uptake of oxygen by the blood passing through the lungs, though it also makes for a lessened efficiency in the release of oxygen to the tissues. A third characteristic of neonatal blood (apparently associated with immaturity of development rather than with adjustment to fetal circumstances) is a deficiency of carbonic anhydrase. This inadequacy is of most significance in premature infants, and tends to retard both the liberation of carbon dioxide and the acquisition of oxygen in the lungs. Thus one respiratory factor is of definite advantage to the infant, one combines advantageous and disadvantageous features, and one can hardly be anything but a liability. In general, the respiratory characteristics of fetal and neonatal blood indicate in various ways the need for a sufficient if not an augmented supply of oxygen to the infant both during and after birth. No evidence suggests that transfusion of adult blood can do harm during the neonatal period; several considerations indicate that such transfusion may be of respiratory usefulness, particularly for premature subjects.

BIBLIOGRAPHY

1. BONAR, B. E., BLUMENFELD, C. M., and FENNING, C.: Studies of fetal respiratory movements; historical and present day observations, *Am. J. Dis. Child.* 55: 1, 1938.
2. BECLARD, P. A.: Recherches qui semblent prouver que le foetus respire l'eau contenue dans l'amnios, *Bull. de la Faculté de Médecine à Paris*, 3: 436, 1813.
3. AHLFELD, F.: Die intrauterine Tätigkeit der Thorax und Zwerchfellmuskulatur. *Intrauterine Atmung*, *Monatschr. f. Geburtsh. u. Gynäk.* 21: 143, 1905.
4. PREYER, W.: *Specielle Physiologie des Embryo*, Leipzig, Grieben, 1885.
5. WEBER, H.: Über physiologische Atmungsbewegungen des Kindes im Uterus. *Inaugural dissertation*. Marburg, 1888.
6. REIFFERSCHIED, K.: Über intrauterine

- terine Atembewegungen des Fœtus, Deutsche med. Wchnschr. 37: 877, 1911.
7. WISLOCKI, G. B.: Experimental studies on fetal absorption, Carnegie Institution of Washington. Department of Embryology. Contributions to Embryology 11: 45, 1920. Contribution 51.
 8. COREY, E. L.: Initial inspiration in mammalian fetus, J. Exper. Zool. 61: 1, 1932.
 9. KLEMPERER, H. H.: Experimentelle Studien zur Physiologie des ersten Atemzuges, Arch. f. Gynäk. 154: 108, 1933.
 10. (a) SNYDER, F. F., and ROSENFELD, M.: Intrauterine respiratory movements of human fetus, J. A. M. A. 108: 1946, 1937.
 - (b) SNYDER, F. F., and ROSENFELD, M.: Direct observation of intrauterine respiratory movements of the fetus, Am. J. Physiol. 119: 153, 1937.
 - (c) ROSENFELD, M., and SNYDER, F. F.: Stages of development of respiratory regulation and changes occurring at birth, Am. J. Physiol. 121: 242, 1938.
 - (d) SNYDER, F. F., and ROSENFELD, M.: Fetal respiration in relation to atelectasis and intrauterine pneumonia, Am. J. Obst. & Gynec. 36: 363, 1938.
 - (e) ROSENFELD, M., and SNYDER, F. F.: Factor of anesthesia in pathogenesis of asphyxia neonatorum, Am. J. Obst. & Gynec. 38: 424, 1939.
 - (f) SNYDER, F. F.: Rate of entrance of amniotic fluid into pulmonary alveoli during fetal respiration, Am. J. Obst. & Gynec. 41: 224, 1941.
 11. BONAR, B. E., and FENNING, C.: Studies of fetal respiratory movements; recording methods, Am. J. Dis. Child. 55: 322, 1938.
 12. EHRHARDT, K.: Atmet das Kind im Mutterleib? München. med. Wchnschr. 86: 915, 1939.
 13. REIFFERSCHIED, W., and SCHMIE-MANN, R.: Röntgenographischer Nachweis der intrauterinen Atembewegung des Fetus, Zentralbl. f. Gynäk. 63: 146, 1939.
 14. (a) BARCROFT, J., and BARRON, D. H.: Genesis of respiratory movements in foetus of sheep. J. Physiol. 88: 56, 1936.
 - (b) BARCROFT, J.: Intra-uterine development of respiratory effort, Brit. M. J. 2: 986, 1939.
 - (c) BARCROFT, J.: The Brain and its Environment, New Haven, Yale Univ. Press, 1938.
 - (d) BARCROFT, J.: Onset of respiration at birth, Lancet 2: 117, 1942.
 15. (a) WINDLE, W. F., and BARCROFT, J.: Some factors governing initiation of respiration in chicks, Am. J. Physiol. 121: 684, 1938.
 - (b) WINDLE, W. F., MONNIER, M., and STEELE, A. G.: Fetal respiratory movements in the cat, Physiological Zoology 11: 425, 1938.
 - (c) STEELE, A. G., and WINDLE, W. F.: Some correlations between respiratory movements and blood gases in cat foetuses, J. Physiol. 94: 531, 1939.
 16. WINDLE, W. F., BECKER, R. F., BARTH, E. E., and SCHULZ, M. D.: Aspiration of amniotic fluid by fetus; experimental roentgenological study in guinea pig, Surg., Gynec. & Obst. 69: 705, 1939.
 17. RUNGE, M.: Die Ursache der Lungenathmung des Neugeborenen, Arch. f. Gynäk. 46: 512, 1894.
 18. SCHMITT, W.: Über die Bedeutung der intrauterinen Atembewegungen beim Fötus, Ztschr. f. Ge-

- burtsh. u. Gynäk. 90: 559, 1926/27.
19. DYROFF, R.: Gibt es regelmässige intrauterine Atembewegungen? Zentralbl. f. Gynäk. 51: 967, 1927.
 20. WINDLE, W. F.: DRAGSTEDT, C. A., MURRAY, D. E., and GREENE, R. R. Note on respiration-like movements of human fetus, Surg., Gynec. & Obst. 66: 987, 1938.
 21. MAHON, R.: A partir de quel âge le foetus peut-il présenter des mouvements actifs? Bull. Soc. d'obst. et de gynéc. 26: 61, 1937.
 22. FITZGERALD, J. E., and WINDLE, W. F.: Some observations on early human fetal movements, J. Comp. Neurol. 76: 159, 1942.
 23. COHNSTEIN, J., and ZUNTZ, N.: Über die Ursachen der Apnoe des Fötus und des ersten Athemzuges beim Neugeborenen, Archiv. f. d. ges. Physiol. 42: 355, 1888.
 24. BARCROFT, J., KENNEDY, J. A., and MASON, M. F.: Oxygen in blood of umbilical vessels of sheep, J. Physiol. 97: 347, 1940.
 25. BARCROFT, J., BARRON, D. H., COWIE, A. T., and FORSHAM, P. H.: Oxygen supply of foetal brain of sheep and effect of asphyxia on foetal respiratory movement, J. Physiol. 97: 338, 1940.
 26. COHNSTEIN, J., and ZUNTZ, N.: Weitere Untersuchungen zur Physiologie des Säugethier-Fötus, Arch. f. d. ges. Physiol. 42: 342, 1888.
 27. SNYDER, F. F.: The oxygenation and carbon dioxide content of fetal blood during the interruption of fetal respiration coincident with the breathing of low oxygen mixtures by the maternal animal, Federation Proceedings 1: 82, 1942.
 28. EASTMAN, N. J.: Foetal blood studies; oxygen relationships of umbilical cord blood at birth, Bull. Johns Hopkins Hosp. 47: 221, 1930.
 29. HASELHORST, G., and STROMBERGER, K.: Über den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta; III. Mitteilung, Ztschr. f. Geburtsh. u. Gynäk. 102: 16, 1932.
 30. COHNSTEIN, J., and ZUNTZ, N.: Untersuchungen über das Blut, den Kreislauf, und die Athmung beim Säugethier-Fötus, Arch. f. d. ges. Physiol. 34: 173, 1884.
 31. HUGGETT, A. S.: Foetal blood-gas tensions and gas transfusion through placenta of goat, J. Physiol. 62: 373, 1927.
 32. KELLOGG, H. B.: Studies on fetal circulation of mammals, Am. J. Physiol. 91: 637, 1930.
 33. ROOS, J., and ROMIJN, C.: Some conditions of foetal respiration in cow, J. Physiol. 92: 249, 1938.
 34. BARCROFT, J., FLEXNER, L. B., and McCLURKIN, T.: Output of foetal heart in goat, J. Physiol. 82: 498, 1934.
 35. EASTMAN, N. J.: Foetal blood studies; chemical nature of asphyxia neonatorum and its bearing on certain practical problems, Bull. Johns Hopkins Hosp. 50: 39, 1932.
 36. HASELHORST, G., and STROMBERGER, K.: Über den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta; I. Mitteilung, Ztschr. f. Geburtsh. u. Gynäk. 98: 49, 1930.
 37. NOGUCHI, M.: Study on gases in umbilical blood, Jap. J. Obst. & Gynec. 19: 328, 1936.
 38. BIDONE, M.: Il contenuto in ossigeno a acido carbonico del sangue dei vasi ombelicali del feto umano durante l'apnea fisiologica, Ann. di ostet. e ginec. 53: 197, 1931.
 39. GOLDBLOOM, A., and GOTTLIEB, R.: Icterus neonatorum; oxygen capacity and saturation of mother

- and fetus, *J. Clin. Investigation* 9: 139, 1930.
40. SMITH, C. A.: Effect of obstetrical anesthesia upon oxygenation of maternal and fetal blood, with particular reference to cyclopropane, *Surg., Gynec. & Obst.* 69: 584, 1939.
 41. KEYS, A.: Carbon dioxide balance between maternal and foetal bloods in goat, *J. Physiol.* 80: 491, 1934.
 42. RIELÄNDER, A.: Der Kohlensäuregehalt des Blutes in der Nabelschnurvene, *Monatschr. f. Geburtsh. u. Gynäk.* 25: 29+182, 1907.
 43. KANE, H. F., and KREISELMAN, J.: Carbon dioxide content of blood in newborn . . . *Am. J. Obst. & Gynec.* 20: 826, 1930.
 44. WILSON, R. A., TORREY, M. A., and JOHNSON, K. S.: Initiation of respiration in asphyxia neonatorum . . . *Surg., Gynec. & Obst.* 65: 601, 1937.
 45. BELL, W. B., and others: The metabolism and acidity of the foetal tissues and fluids, *Brit. M. J.* 1: 126, 1928.
 46. EASTMAN, N. J., GEILING, E. M. K., and DELAWDER, A. M.: Foetal blood studies; oxygen and carbon-dioxide dissociation curves of foetal blood, *Bull. Johns Hopkins Hosp.* 53: 246, 1933.
 47. ROOS, J.: Respiratory problems in foetal life. The oxygen dissociation curves. *Kongressbericht 1, des XVI Internationalen Physiologen-Kongresses.* Zurich, 1938.
 48. DARROW, R. R., NOWAKOVSKY, S., and AUSTIN, M. H.: Specificity of fetal and of adult human hemoglobin precipitins, *Arch Path.* 30: 873, 1940.
 49. HAUROWITZ, F.: Die Hämoglobine des Menschen, *Ztschr. f. physiol. Chem.* 232: 125, 1935.
 50. JONGBLOED, J.: Spectrophotometer investigation into differences between foetal and maternal hemoglobin in man, *J. Physiol.* 92: 229, 1938.
 51. WINDLE, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders, 1940.
 52. BARCROFT, J., ELLIOTT, H. R. E., FLEXNER, L. B., HALL, F. G., HERKEL, W., MCCARTHY, E. F., MCCLURKIN, T., and TALAAT, M.: Conditions of foetal respiration in goat, *J. Physiol.* 83: 192, 1934.
 53. HASELHORST, G., and STROMBERGER, K.: Über den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta; II. Mitteilung, *Ztschr. f. Geburtsh. u. Gynäk.* 100: 48, 1931.
 54. NOGUCHI, M.: On the oxygen dissociation curve of haemoglobin in umbilical blood of new-borns, *Jap. J. Obst. & Gynec.* 20: 358, 1937.
 55. DARLING, R. C., SMITH, C. A., ASMUSSEN, E., and COHEN, F. M.: Some properties of human fetal and maternal blood, *J. Clin. Investigation* 20: 739, 1941.
 56. JONXIS, J. H. P.: Presence of fetal hemoglobin in young nursing, *Maandschr. v. kindergeneesk.* 6: 356, 1937.
 57. STEVENSON, S. S.: Carbonic anhydrase in newborn infants, *J. Clin. Investigation* 22: 403, 1943.
 58. MELDRUM, N. U., and ROUGHTON, F. J. W.: Carbonic anhydrase; its preparation and properties, *J. Physiol.* 80: 113, 1933.
 59. BARCROFT, J., and YOUNG, I. M.: Oxygen in the blood emerging from the brains of post-mature foetal rabbits, *J. Physiol.* 102: 25 P, 1944.

Chapter III

RESPIRATION: NEONATAL ASPECTS

Section 1 . . .	The Onset of Breathing at Birth
Section 2 . . .	Effects and Duration of Anoxia at Birth
Section 3 . . .	The Physical State of the Neonatal Lung
Section 4 . . .	Mechanical Forces in Early Respiration
Section 5 . . .	Clinical Manifestations of Respiratory Adjustment After Birth
Section 6 . . .	Rate, Volume, and Regularity of Breathing in the Neonatal Period
Section 7 . . .	Clinical Summary

THE ONSET OF BREATHING AT BIRTH

MUCH ANIMAL and some human evidence indicates that the fetus tends to breathe on occlusion of the cord, a physiologic insult which, whatever the dissociation curves, must immediately and progressively diminish fetal oxygen and elevate fetal carbon dioxide. The mass of evidence suggests that respiratory onset follows as effect from cause. Why then in the asphyxiated non-breathing baby should these very chemical stimuli which should induce vigorous respiration fail to be effective? Probably the correct explanation for this contradiction was offered by Schmidt¹ and repeated by Eastman,² that conditions which should stimulate the respiratory center may, if present in excess, have a reverse or depressant effect upon it. Thus, one can think somewhat diagrammatically of three zones of human fetal existence. In the first or usual zone, the blood oxygen is a little lower and the carbon dioxide a little higher than in the mother's blood. In this zone the fetus makes no attempt to breathe, a circumstance for which some sluggishness of the respiratory centers has to be postulated. In the second zone are those greater diminutions in oxygen and (perhaps) increases in carbon dioxide tensions which call forth respiratory response whether *in utero* or at birth. The third zone is one of still greater anoxia, in which the respiratory centers become incapable of normal (or of any) activity. Whether increase in carbon dioxide shares with anoxia in bringing about this unfavorable situation is

not certain. Excess in carbon dioxide tension is undoubtedly present. Finally, it must be remembered in attempting to explain individual instances of clinical asphyxia in terms of bio-chemical reasoning, that human infants not behaving normally may have been subjected to damaging experiences at some time preceding actual birth, and that operative and anesthesial effects incidental to delivery may have altered the respiratory center's sensitivity to what are ordinarily potent stimuli.

In the present state of our knowledge, it seems justifiable to believe that human life *in utero* does have its periods of rhythmical activity of the respiratory apparatus, perhaps brought about by minor departures from the usual adjustments of the respiratory gases. Inasmuch as they can not be proved to occur in all human infants before birth, these periods of respiratory movement can hardly be considered essential forerunners to the assumption of extra-uterine breathing. In the absence of any better substantiated evidence, the onset of breathing after birth must be traced to stimuli incidental to separation from the maternal organism. The question whether these stimuli are merely the direct activities of an excess of carbon dioxide molecules or of a deficiency of oxygen molecules in the medullary respiratory center needs further discussion in the light of recent advances in physiology.

The newer knowledge of reflex regulation of breathing, as it has emerged from the work of Heymans,³ Schmidt,⁴ Comroe,⁵ and many others has been well summarized by Schmidt¹ in MacLeod's *Physiology in Modern Medicine*. It has been shown that although the "respiratory center" in the medulla is ordinarily sensitive to changes in carbon dioxide tension in the blood, the chemo-receptors in the aortic and (particularly) the carotid bodies furnish "a reflex drive to the center when the latter unaided is unable to prevent relatively marked and potentially dangerous changes in the chemical composition of the arterial blood." Among the conditions under which this is most likely to occur, Schmidt places anoxia first, but mentions also "derangement of the reactivity of the medullary center to changes in its environment, as by anoxia, trauma, disease, or particularly by narcotic drugs, and poisoning by metabolic acids"¹ as in uncompensated acidosis. This statement obviously describes in some respects the situation of all infants upon the moment of birth, while the status of the occasional infant who has been exposed to more than the average hazard in the way of trauma or drugs is characterized especially accurately. The newborn infant is thus a classical illustration of an organism whose respiration might be expected to be under the control of the carotid and aortic

reflex mechanisms. These mechanisms, it may be stated in passing, are particularly responsive to oxygen lack,⁶ so that it might be possible to depress or even to stop the breathing by purveying a considerable excess of oxygen to the organism under such circumstances. Schmidt¹ points out on a later page that Snyder and Rosenfeld believe the carotid body to be inactive in the infant at birth, but also that the response of the infant to lobeline (as advocated by Wilson, Torrey, and Johnson⁷) is through the carotid and aortic mechanisms. Clinical experience has shown a powerful effect in many not too severely asphyxiated infants following the injection of lobeline; experience has also shown that the more profound the state of asphyxia the less likely is lobeline to produce any effect. The same statements may be made regarding coramin (nikethamide), and the site of action of this drug is similar to that of lobeline.⁸ It seems probable that the fetal and newborn medullary center is in, or at least bordering upon, a state of depression at normal delivery and that these more recently studied mechanisms are in control of breathing. If the infant is apneic and does not begin to breathe (or to breathe better in response to lobeline), the probability is not that this extra-medullary chemo-receptor system is undeveloped but that the disturbance has become so great as to destroy the responsiveness of that system. Not only the regular but also the emergency mechanism is wrecked. Nevertheless the carotid and aortic bodies may represent specially useful provisions by means of which perhaps the majority of not too severely asphyxiated infants manage to begin breathing.

EFFECTS AND DURATION OF ANOXIA AT BIRTH

Fetal and neonatal subjects have long been recognized as able to withstand degrees of anoxia intolerable or much less tolerable to the adult organism. Observation testifies to the fact that human babies that have not breathed for more than ten minutes after delivery may be revived, sometimes to an existence which proceeds entirely normally. On the other hand, the adult who has failed to breathe or has otherwise been totally deprived of oxygen for seven or eight minutes does not breathe again. Feldman⁹ recounts Brown-Sequard's experiments in which removal of the medulla from adult animals produced death in less than three and one-half minutes, while newborn members of the same species did not die for 30 to 46 minutes. Paul Bert¹⁰ satisfied himself that this peculiarity of neonatal tissues does not last long after birth. Recent workers^{11,12} have been intrigued by the same problem. Mice aged one day have been shown to be still alive after 44 minutes of exposure to pure carbon

monoxide, while in adult mice no heart beat was perceptible after less than a minute in the same atmosphere. The circulation of mice aged six days stopped after being so exposed for 8 minutes. A similar relationship of survival time appeared in mice placed in pure hydrogen or pure carbon dioxide. In rats of 6 days the resistance to oxygen deprivation appears to be greater than that of the adult, but by about the tenth or twelfth day the young and older animals are indistinguishable in this regard.

Himwich and his colleagues¹³ have found that if newborn dogs are made to inhale pure nitrogen their arterial blood samples lose all detectable oxygen within five minutes, yet the animals continue to survive for as much as half an hour or more, this survival being accompanied at first by respiratory movements, and, after these cease, by cardiac activity for somewhat longer. More interesting perhaps is the experimental observation by these workers that puppies aged 1 and 12 days can tolerate 5 per cent oxygen in nitrous oxide for at least 3 hours, although the oxygen in the blood remains at only 4 or 5 volumes per cent during this time; in the same atmosphere adult dogs can survive only 10 to 15 minutes. Selle and Witten¹⁴ have found that not only is such a primitive mechanism as gasping retained much longer by the asphyxiated newly born rat than by the older animal, but also other responses such as pupillary responses of the isolated head, trunk reflexes of the spinal animal, and the beating of the exposed heart, "are all retained longer the younger the animal." Measurements of the oxygen consumption of various parts of the brain during growth have been interesting¹⁵ both as they show the oxygen consumption to be very low in the rat's brain from birth till an age of four or five weeks, and also in the demonstration that tissues from various brain levels are found to differ from one another in this regard as growth proceeds. Thus the cerebellum and medulla have the greatest uptake in the first three weeks, while that of the cortex is lowest; with growth these characteristics gradually become reversed. Himwich and his co-workers¹⁶ believe that "factors which may contribute to make the newborn relatively tolerant to anoxia are 1, low cerebral metabolic rate; 2, poikilothermia, and 3, anaerobic source of energy." There is evidence that if the anaerobic use of blood sugar be denied to fetal animals their survival time under anoxia is no better than that of adult animals.

There is a consistency about all the information obtainable experimentally on this general point. How should it be applied to the physiology of the human infant? Evidence is available to show that with birth the infant is emerging from a state of much

lower oxygen demand than that of the adult. Probably some persistence of this condition lingers into the first minutes or hours of extra-uterine existence, even though a phase is being entered during

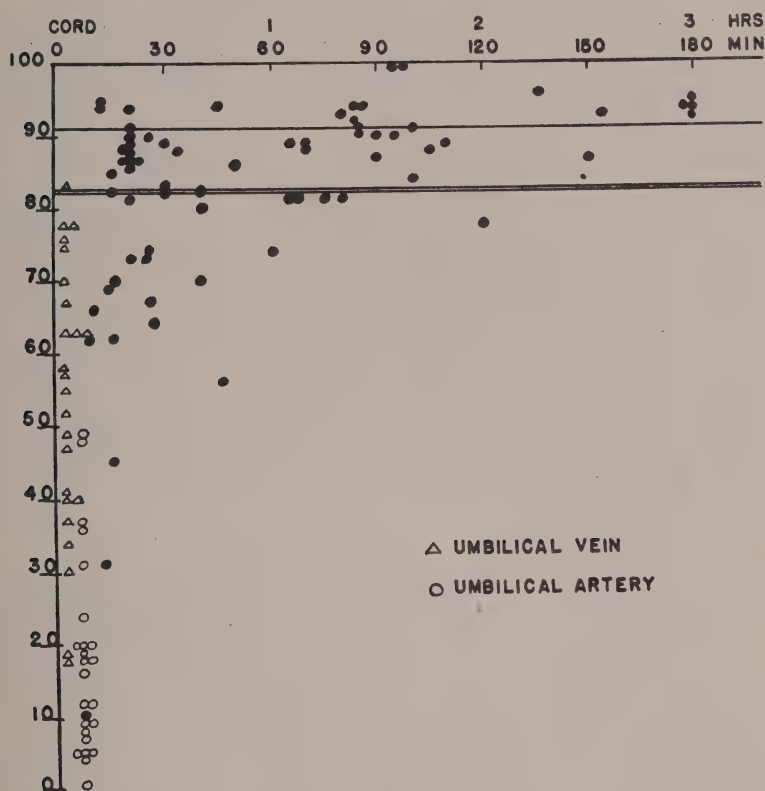


FIGURE 5

Post-natal oxygen adjustment of arterial blood. One hundred twenty-one determinations made at various intervals during 3 hours after birth in 31 infants. The triangles and circles are from cord specimens, the solid dots arterial (cutaneous) specimens. Vertical scale = percentage O₂ saturation; horizontal = time after birth. Single line at 91% is lowest level normally found in arterial blood of adults; double line at 82% indicates level below which cyanosis might be expected. (Smith, Kaplan, *Am. J. Dis. Child.*, 64: 843, 1942.)

which the oxygen requirement is greater in proportion to body size than the requirement of adult life. Certain observations seem to agree with this supposition. Brinkmann and Jonxis¹⁷ have collected a few measurements of the oxygen content of arterial blood in the very young. The general impression made by their data is of life proceeding apparently normally at oxygen saturations which

might be expected to produce symptoms in older children. Levels as low as 77 per cent O_2 saturation were discovered in the arterial blood of infants who manifested no evidences of dyspnea or cy-

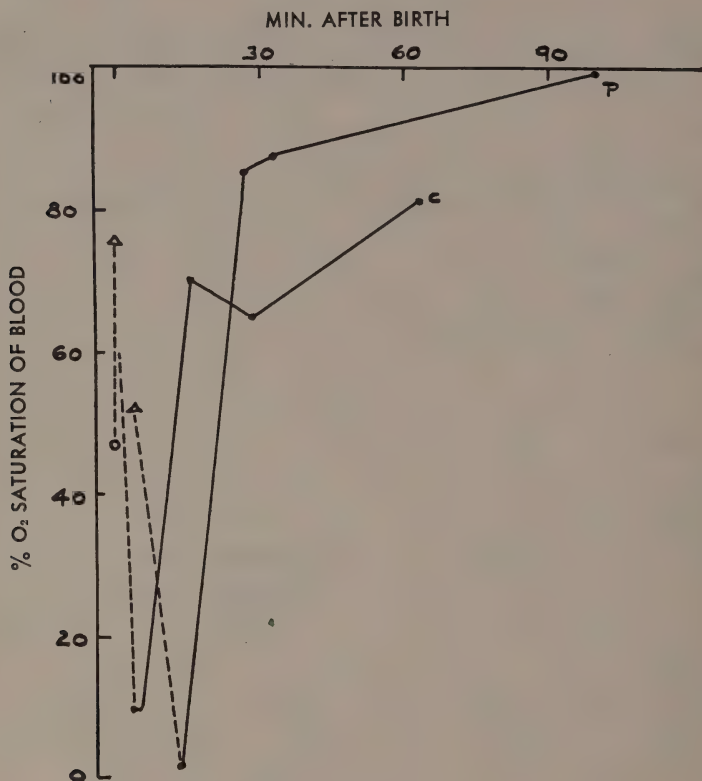


FIGURE 6

Course of post-natal oxygenation in the arterial blood of two infants. Reasonably satisfactory oxygenation is attained even though Infant C did not breathe for 7 minutes; Infant P for 14. Triangles indicate umbilical vein specimens; clear circle, umbilical artery; solid dots arterial (cutaneous) blood. Roentgenograms of these infants are shown in Figures 9-12. (From data of Smith and Kaplan¹⁸.)

anosis, while still lower values appeared in apparently normal pre-matures.

Another study¹⁸ of the general schedule of post-natal oxygen adjustment (Fig. 5) has shown how rapidly and efficiently the blood oxygen content may be re-established in infants who have undergone periods of seven or even fourteen minutes of complete apnea after birth (Fig. 6). These particular infants are known to have

made apparently normal subsequent progress in development, which is testimony to their ability to withstand anoxic insult. However, one is curious as to the later growth and development of every such infant, and particularly as to the later life of those experimental animals whose survival after very prolonged periods of experimental anoxia is described in the preceding paragraphs. In at least one study¹⁹ permanent central nervous system damage has been demonstrated in young animals subjected to anoxia of perhaps 20 minutes duration at term. Schreiber and others²⁰ have collected much evidence to indicate that the human central nervous system, although capable of survival after anoxemic insult may often be thereby rendered incapable of achieving normal function. It is perhaps reasonable to speculate whether such resistance to anoxia as probably occurs in the human fetus and infant may not be something of a mixed blessing; it may diminish or retard the appearance of those danger signals which warn the obstetrician of anoxic crises, and it may allow the infant to exist as a damaged individual after an interlude which would have caused the death of an adult organism. Nature seems to have made provision for the survival of the species at a cost of incomplete development of some of its members.

THE PHYSICAL STATE OF THE NEONATAL LUNG

The question of intra-uterine respiratory motion can not be closed without discussion of the effects of such activity on the fetal and thus the neonatal lungs. Obviously even occasional respiratory movements could scarcely occur without drawing a portion of whatever surrounds and fills the nose and mouth into the smaller air passages and alveoli. This aspiration seems so "pathological" a process that workers have been reluctant to accept the idea of amniotic fluid passing beyond the trachea. Reifferscheid²¹ believed persistent closure of the epiglottis kept the lungs intact throughout gestation. Cohnstein and Zuntz²² invoked the *Tauch*, or, as it might be translated, the "immersion" reflex in this connection. Mentioned in various applications by Schiff, Holmgren, Paul Bert, and others, this reflex checks the respiration of a tracheotomized animal when its nostrils are moistened with water. Cohnstein and Zuntz reasoned that any respiration before birth, with its consequent drawing of fluid into the upper air passages would be immediately stopped by the operation of this mechanism. Indeed, they considered their observations on young (but not fetal or neonatal) animals had substantiated this argument. Once the fetus was born into the air, they reasoned that a release would take place by virtue of drier surroundings. Enough fetal animals have been observed in

rhythmic respiratory motion *in amnio* since the time of Cohnstein and Zuntz so that the application of the *Tauch* reflex to fetal physiology must be denied.

Walz²³ has suggested that whether or not amniotic fluid is aspirated, the negative pressure in the fetal thorax is an important regulator of fetal circulation. Granting that they arise under asphyxial situations, respiratory movements might thus have value in drawing oxygenated fetal blood up the umbilical vein from the placenta by virtue of the diminished intrathoracic pressure produced. Of this there has been no proof; in fact, a considerable argument against the hypothesis has been delivered by Schmitt.²⁴ Yet workers continue to search for a theoretical advantage to the organism from the movements of fetal respiration, so deeply ingrained is the notion that such movements occur normally *in utero* and so anxious are they to assign a useful purpose to fetal respiration. Snyder and Rosenfeld²⁵ have stressed the idea that, far from having a noxious effect, the inhalation of amniotic fluid is of direct assistance to the fetal lung, aiding in its structural differentiation and causing dilatation of alveoli which might otherwise arrive at term in a state of inefficient collapse. Interference with such aspiration by virtue of mechanical obstruction to the bronchioles in fetal life is, according to these authors, a cause of atelectasis. The normal functioning of such a process would cause the organism to be born with liquid-filled alveoli, but these are considered to be more satisfactory than alveoli completely collapsed. Alveoli distended by amniotic fluid could be converted into air-containing spaces by rapid further expansion immediately after birth, more pulmonary epithelium thus becoming available for contact with air than remaining covered with fluid. So the process might continue with the gradual absorption of the liquid.

Undoubtedly, some such process must take place after the first breath in any infant, but the essential character of amniotic fluid as an entering wedge for expanding the fetal lung can not be urged unless we know that all fetuses make sufficiently frequent and regular respiratory movements to utilize the aspirated amniotic fluid for this purpose. Of this there is doubt, increased by the recent observations upon animals by Shock²⁶ and by Whitehead, Windle, and Becker.²⁷ This doubt also applies to accepting respiratory movement as an essential activity of the human fetus. Moreover, instances have been reported of well-developed alveoli in portions of human lungs where tracheo-bronchial communications with the amniotic environment were occluded by congenital malformations.²⁸

Another and a less theoretical approach to an understanding is by examination of the lungs of young infants for evidences of obvious amniotic fluid. Results of such studies must be interpreted with the reservation that the only lungs which become available are of necessity from infants who have died and are thus not in "physiological" condition. Such deaths must usually have been asphyxial. Moreover, normal infants have a considerable opportunity to aspirate amniotic fluid present in the mouth and nose at the time of the first extra-uterine breaths, and there is no way to distinguish this from fluid inhaled during intra-uterine existence.

Farber and Sweet²⁹ examined microscopically the lungs of 124 infants who died before five weeks of age. They could find no traces of amniotic detritus in 12 per cent, while 15 per cent (most of whom had succumbed at three days or less) showed large amounts. The remaining majority showed evidence of some inhalation of amniotic fluid, but usually in small amounts which may well have been inhaled after birth. The import of this study is that the majority of infants who aspirate amniotic sac contents may do so merely by the act of early extra-uterine breathing; a few never inhale any; a few inhale much, but usually as a consequence of pathologic circumstances. Szlavik³⁰ examined the lungs from 36 infants succumbing from various causes before the age of eight days (16 of them stillborn) and found evidences of aspirated amniotic fluid in every instance. The clinical histories of these patients were such as to suggest the presence of amniotic fluid as normal to the newborn lung. Since the aspiration of amniotic fluid was until recently considered an evidence of intra-uterine asphyxia and by no means a normal circumstance, the matter has considerable medico-legal importance, and Camerer³¹ has considered another series of postmortem studies from this viewpoint. His material consisted of lungs from 212 infants; 70 of the subjects had succumbed within a few moments after birth with lungs "not absolutely airless," while the remaining majority had survived during the first twenty-four hours. Evidences of amniotic fluid were found in the lungs of all but three infants, in circumstances which led the author to conclude that the liquid was aspirated by periodic intra-uterine thoracic and diaphragmatic movements. Therefore only when unusual quantities of this material are found should that *per se* be regarded as a cause of death, or on the other hand, as a result of intra-uterine difficulty. Most infants thus seem to begin their extra-uterine existence with more or less amniotic fluid in their lungs. How long this has been present is still a matter of dispute; that it has served any useful purpose appears to be unlikely. But whether much, little, or

any flow of amniotic fluid into and out of the lungs is maintained by fetal movements of the respiratory muscles, there remains a physiological problem which the respiratory apparatus must meet at birth. This is the expansion of the lungs with air.

MECHANICAL FORCES IN EARLY RESPIRATION

At the time the infant emerges from the birth canal the lungs are soggy, more or less collapsed, their air spaces containing fluid (if anything), so that the simple test of the floating or sinking of the lung in water is the traditional indication of whether respiration—in the common sense of the word—has occurred. They lie in a more or less collapsed and atonic thorax, with its walls hollowed inwardly (Fig. 9) which within a comparatively short space of time must convert them into buoyant, air-containing organs. The comparison between a water-filled and an air-containing sponge is helpful, particularly if one notes certain differences. Water squeezed from a sponge simply drains away, and the released sponge by its structural resilience expands to its original size, becoming filled with air in the process. The newborn lung, however, not only lacks this direct peripheral egress for whatever liquid it contains, and it also lacks the resilience of the sponge; it has little power in itself of re-expanding to its fetal dimensions, and none of expanding beyond them.

It is clear that the lungs inflate because of the total inspiratory force of the ribs, sternum, cartilages, inter-costal muscles, and diaphragm. This force acts by creating a negative pressure in the closed and empty pleural spaces, which in turn exerts tension on the surfaces of the lungs. To this force is opposed the important resistance of the lungs themselves. To return to the analogy of the sponge, the effect is somewhat as though circumstances required that a sponge be pulled out to larger dimensions than it had ever previously occupied. Two factors resist the distension of the newborn lung: (1) the elastic tissue and smooth muscle of the pulmonary parenchyma, and (2) the cohesion of moist surfaces or fluid-containing spaces composing the bronchial and alveolar system of the fetal lungs. If the principal opposed factors are mechanically assessed, one learns how much negative pressure the infant's thorax can bring to bear on the lung surfaces, and what margin of safety lies between this and the amount of counter-acting resistance imposed by elastic and muscle tissue and by cohesion in the lungs.

On the latter side of the balance, there is reason to believe that the alveolar cohesion factor is much more important than the resistance contributed by the smooth muscle and elastic tissue, and

that the sum of the two may be an initial resistance equal to the weight of 20 to 30 cm. of water (or 15–22 mm. Hg).³² Hermann,³³ who first investigated the subject in 1879, approached it because of curiosity as to why the thorax remained permanently expanded after the first breath or after artificial insufflation, a puzzle which intrigued several earlier authors. Hermann worked largely with the lungs of full-grown rabbits, in which he attempted to induce a state comparable to fetal collapse first by simply opening the thorax and later by subjecting the lung surfaces to positive pressure. He said he found that pressures even as great as 840 mm. Hg (over 1000 cm. water) applied to the surfaces would not completely collapse the lung, a certain amount of minimal air remaining trapped in the alveoli after the bronchial lumina had been closed by the pressure from without. He finally resorted to the production of complete collapse by filling the lungs with an absorbable gas (CO_2), and allowing that to be completely removed. After this process, the lungs being entirely free of any gas or air, he considered them to be similar to those of the newborn organism. Hermann found that air had then to be blown into the trachea under pressures of from 12 to 20 cm. of water in order to expand the alveoli. Once the expansion had taken place (or before complete collapse had been brought about by the CO_2 absorption), the same lungs could be expanded by the insufflation of gas under pressures of 3 to 9 cm. water. The excess pressure required to overcome complete collapse was assumed by Hermann to have resulted from adhesion and sticking together of the bronchial and alveolar walls.

The subject was studied much more completely and definitively by Wilson and Farber³⁴ part of whose work was also with lungs removed from rabbits. They were able to make pressure determinations upon the lungs in the living animal as well, and having correlated mechanical studies upon lungs in living and dead animals, the authors applied their method to lungs removed at autopsy from premature and full-term infants, either stillborn or dead shortly after birth from non-pulmonary causes. The lungs were subjected to rhythmical and regulated negative pressures, the resultant excursion of air in and out of the trachea being recorded by a spirometer. The results showed a considerable similarity to those of Hermann, in that the lungs of still-born infants, or those removed at post mortem from live-born infants (or animals) and then subjected to collapse by mechanical procedure, required negative pressures of 15 to 25—and sometimes 35—cm. of water upon their surfaces before significant expansion took place. These forces are definitely above the 12 to 15 cm. used in maintaining artificial respiration in

adults in the Drinker respirator. However, as with Hermann's material, once the alveoli had been appreciably expanded under such tensions, it became possible to produce a comparatively improved "respiration" by the rhythmical use of lower negative pressures which had not previously been effective in drawing air into the lungs. As Wilson and Farber concluded from this evidence, "The first breath of a new-born baby may thus be its most difficult one. For a variable period after birth, especially vigorous inspirations must be maintained."

The inspiratory force available to the newborn human infant has been measured more or less accurately by placing a mask over the infant's nose and mouth and connecting it by wide tubing to an adjustable obstruction.³² With the obstruction gradually closed, the baby was forced to call upon his thoracic structures for greater positive and negative pressures in order to continue breathing; these were measured by a manometer connected just beyond the mouth, which thus gave a record of the intra-pulmonary forces attainable by the infant thorax. The respiratory apparatus of most infants and even of some prematures was found capable of exerting negative (and positive) pressures of 40 to 50 cm. of water. The maximum effort of the average adult in inspiration brings about an intra-pulmonary negative pressure of perhaps 95 cm. of water, so that the power of the neonatal thorax is somewhat surprising. It may be allowable to draw conclusions from these data as to the proper use of force in "resuscitating" the newborn infant. Mechanical devices which either blow air or other gases into the upper air passages or produce a negative pressure around the thorax may be expected to do little damage to the lung tissues or vessels, provided they stay within the range of forces applied by the normal thorax and diaphragm. Thus, since the infant normally is able to exert an intra-pulmonary pressure of -40 cm. of water while struggling and crying, it would seem reasonable to use, if necessary, forces up to that amount in assisting the infant who fails to breathe.

It becomes clear from such studies that the change from the fetal to the normal extra-uterine state of the lung can hardly be a matter of the first moments of life, nor, often, even of the first few days. It seems strange that a prolonged controversy was waged fairly recently on this point, Ungar,³⁵ as late as 1909 having maintained that the lungs fully expand immediately after birth. An interesting review is presented by Farber and Wilson.³⁶ The artificial inflation of the lungs of newborn infants as carried out by these authors, and by others³² using the same method, has given the opportunity of directly observing the mechanism of expansion and watching

the irregular and patchy fashion by which it almost always proceeds.

CLINICAL MANIFESTATIONS OF RESPIRATORY ADJUSTMENT AFTER BIRTH

Direct observations are in general agreement with most radiologic findings as to the sites of earliest post-natal inflation. These are most often the areas toward the anterior lung margins^{36,37} whereas the regions toward the base and the paravertebral and central portions may remain airless much longer. It is probable that the mere thinness of the lung lappets makes them more responsive

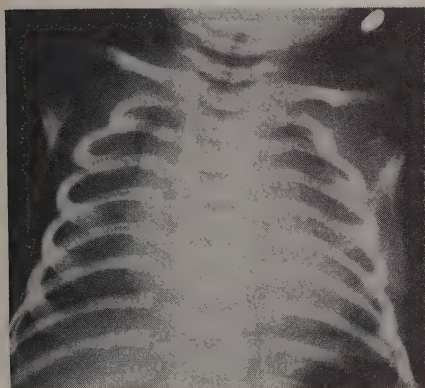


FIGURE 7

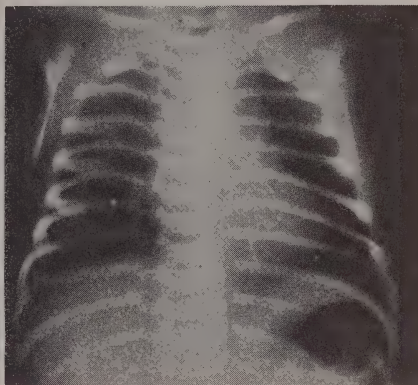


FIGURE 8

Figures 7 and 8 are roentgenograms of the same normal infant aged 10 days, taken in extreme expiration and inspiration.

The characteristic conical shape of the neonatal thorax, the horizontal direction of the ribs, and the marked difference in cardiac and mediastinal outlines depending upon phase of respiration, are apparent.

to negative pressures exerted upon opposite surfaces not separated by large masses of pulmonary tissue, as is the case centrally and at the bases.

In the course of the description just presented care has been taken to avoid using the word "atelectasis." Much confusion has arisen in the past because of this term and the connotations of pathology and of resorption of air from the lungs which have become attached to it. Actually the lungs of all infants have to be atelectatic at birth and persist in being more or less so for varying periods of time, unless they be immediately inflated with the first inspiration, as has been stated to be unlikely. The division between atelectasis of this physiologic nature and atelectasis of a pathologi-

cal degree can be drawn with difficulty, and perhaps had best not be drawn at all. The persistence of the roentgen appearance of unexpanded lung tissue, or (what is somewhat more difficult to demonstrate), its physical findings, is of clinical importance largely in accordance with the presence or absence of other signs of disease or debility.

Roentgenograms of the neonatal chest give interesting informa-

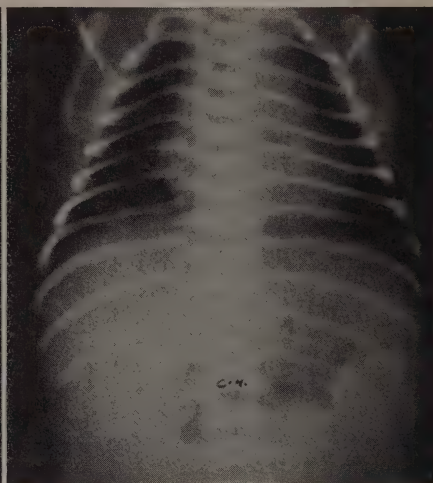
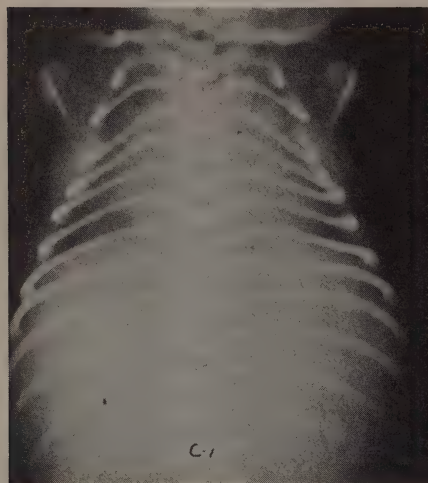


FIGURE 9

FIGURE 10

Figures 9, 10, 11, 12, show the post-natal pulmonary expansion of the two infants whose blood oxygenation is shown in Figure 6.

tion regarding continuation of this fetal state into extra-uterine existence. The degree of unexpanded lung or of atelectasis, the frequency with which it is observed, and the period during which it persists have been variously reported in various studies. It is difficult to understand how one group of observers³⁸ could find no evidence of atelectasis during the first 14 days of life in 24 of 25 normal infants, or how others could report complete aeration in the thoraces of more than 150 infants less than 48 hours of age.³⁹ Solis-Cohn and Bruck,⁴⁰ in a considerably larger group of infants examined during the first week found areas of atelectasis present in 4 per cent at some time or other. In contrast to these figures, films taken at the Boston Lying-In Hospital have shown unexpanded areas in the lungs of 18 per cent of infants roentgenographed between the ages of 6 and 13 days of life. Why this number should be so comparatively great is difficult to understand unless criteria for diag-

nosis are different, but the fact that these subjects had lived at least a week and that films were made as part of a routine pre-discharge examination indicates that they may be considered a normal group of infants.

These data may be compared with the findings published by

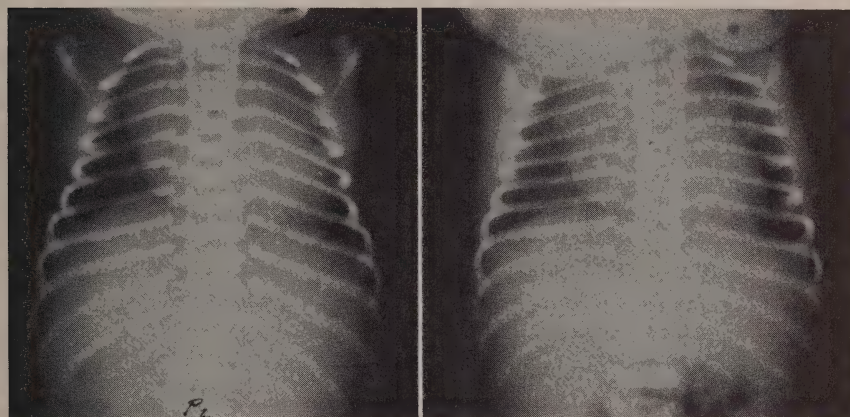


FIGURE 11

FIGURE 12

Fig. 9. Infant C. 1 minute after birth, 6 minutes before breathing.

Fig. 10. Infant C. 60 minutes after birth. Blood $\pm 80\%$ oxygenated.

Fig. 11. Infant P. 18 minutes after birth, 4 minutes after breathing.

Fig. 12. Infant P. 99 minutes after birth, 85 minutes after breathing. Blood $\pm 100\%$ oxygenated.

(Smith, Kaplan, *Am. J. Dis. Child.* 64: 843, 1942.)

Dunham and D'Amico,⁴¹ from films of 33 infants made at regular intervals from the first hour until the 10th day of life. No percentages are tabulated, nor can they be exactly calculated from these authors' data, but the impression is given that aeration was "good" in only about half the lungs even at the tenth day. This work contains a helpful and interesting discussion of the roentgenological peculiarities in the newborn, among them the great difference in radiolucency of the lung fields at inspiration and expiration during the first week. The almost complete cloudiness of the entire lung fields in expiration suggested to these authors that "the residual air of an infant is very meager, even as late as the tenth day of life." Figures 7 and 8, from a normal infant of 10 days illustrate the same point.

Actually a considerable degree of unexpanded lung is compatible with proper oxygenation of the blood. In a study of the increasing oxygenation of the infant's blood immediately after birth¹⁸ simul-

taneous roentgenograms and measurements of arterial blood oxygen have shown that adequate pulmonary function does not necessitate complete expansion of all portions (Figs. 9, 10, 11, 12) so that there is obviously a considerable margin of safety within which the partially expanded lung meets the body's demands upon it.

In practice it is not uncommon to observe newborn infants, often those considerably damaged at or before birth, managing to survive for some hours although their lungs give clinical evidence of no expansion whatever, and when examined postmortem reveal no inflated alveoli. This situation is often observed in non-viable premature infants; it is especially frequent in wards where (quite properly) free use is made of tents and chambers to surround the asphyxiated newborn patients with very high partial pressures of oxygen. Even a short period of survival with completely inadequate pulmonary function bears witness to the margin of safety just mentioned. The phenomenon must arise in some part from the fetal acclimatization to anoxic circumstances mentioned on page 33, but it indicates also that a certain amount of oxygen must diffuse into the blood through the tracheal, bronchial and bronchiolar epithelium, and it calls for a brief consideration of the possibility of gastro-intestinal and cutaneous oxygen absorption.

There is no reason to suppose the air which enters the gastro-intestinal tract with the earliest inspiratory effort to be different from that which enters the lungs. Since several hundred cubic centimeters may often be thus swallowed or "inspired" into the stomach, a considerable quantity of oxygen might be taken up from this region by the blood. Dillon⁴² describes an infant who survived for five hours with completely airless lungs but an air-filled stomach and upper bowel. It is highly probable that life was to some extent supported by this mechanism.

Krogh⁴³ cites figures for oxygen and carbon dioxide diffusion through the integument of such animals as reptiles, frogs, and eels. The diffusion is greater with increased body temperature and coincidentally increased peripheral circulation. It is greater in the case of thin surfaces than thick and coarse ones, though it is a triumph for the possibility of cutaneous respiration that a very small amount of oxygen enters even the tortoise through its surface. Oxygen exchange through the integument is of course governed also by the difference of tension between the blood and the atmosphere. In the infants under consideration the former value is abnormally low, while the latter may be artificially greatly increased, so that a steep gradient is possible. For the oxygen tension

of the ordinary atmosphere Krogh⁴⁴ has published the following data:

CUTANEOUS RESPIRATION PER SQUARE DCM. OF SURFACE

	O ₂ Maxi- mum	O ₂ Mini- mum	CO ₂ Maxi- mum	CO ₂ Mini- mum	Observer
Man	—	0.5	—	1.18	Gerlach
Man	—	—	3.1	0.94	Schierbeck
Pigeon	0.92	0.47	1.1	0.60	Krogh
Tortoise	0.1	—	0.15	—	Krogh
Frog	1.8	1.51	5.3	3.0	Krogh
Frog	2.1	1.62	4.4	3.1	Krogh
Eel	1.05	0.4	—	—	Krogh

In 100 per cent oxygen it should be possible to supply a human organism with at least 2.5 cc. O₂ for the same unit of surface per hour, so that a newborn infant with a skin surface of about 23 square dem. should absorb even under these favorable circumstances about 1 cc. of oxygen per minute. Granting the infant a thinner integument than that of the adult, even one so thin as that of a frog, the total cutaneous respiration could only be about 2 to 3 cc. to apply toward a need approaching 25 cc. per minute (see Chapter 7). Experimental data on the effect of surrounding the body of an anoxic infant with 100 per cent oxygen would, nevertheless, be worth seeking.

Certain phenomena are usually observable and detectable by mensuration as the thorax develops under the various influences of the first days of life. Scammon and Rucker⁴⁵ have described and discussed the main changes in volume and proportion. The thorax deepens from front to back, often at times developing a greater antero-posterior than lateral diameter for a short time, and with the first breath its circumference expands, only to decrease again in a period of post-natal circumference loss which lasts for perhaps three days. This diminution in circumference may only be a decrease in soft-tissue substance, a part of the general physiological weight loss, for it parallels that phenomenon and is usually restored by about the twelfth day. Certain surface manifestations of internal pressure changes are often visible with the individual breaths, particularly those deeper ones associated with crying. Normal inspiration involves the simultaneous elevation of the ribs and downward pull of the diaphragm; the latter structure must have if not an expanding anchorage at least a resistant one from which to exert its traction. But in the newborn, and more characteristi-

cally in the premature infant, the ribs, cartilages, and intercostal muscles are so weak that each contraction of the diaphragm may pull the line of its attachment inward, so that a furrow appears on the outer wall of the chest. It has been reported ⁴⁶ that the same infant may at times expand the chest and lower the diaphragm simultaneously, while at other times the chest wall contracts as the diaphragm comes down. In particularly immature infants or during strong inspiration with crying, one often observes the entire sternum and much of the anterior chest to retract, an indication not only of diaphragmatic contraction but also of the resistance opposed by the state of the lungs to attempts at their inflation. Even in large and robust newborn babies almost all of the actual expansion of the thoracic cavity with each inspiration is done by the diaphragm; the anterior and lateral walls of the thorax can be shown by photographs to do little more than hold the position they attained in the first few minutes after birth, and to undergo very little excursion.⁴⁷⁻⁴⁹

RATE, VOLUME AND REGULARITY OF BREATHING IN THE NEONATAL PERIOD

The difficulties involved in making even the simplest measurements during neonatal life are strikingly illustrated by the number of papers that have been published concerning the rate and volume of breathing at this period. It has taken some forty years to establish what are probably normal values. On certain points such as the vital capacity there is as yet no definite knowledge, nor indeed the likelihood of any except insofar as indirect approaches allow estimates to be made.

The respiratory rate has been the subject of study since—if not before—the work of Dohrn⁵⁰ in 1895. The simple method of observing the infant and counting its respiratory movements has rarely been relied upon; where it has been used the counts are too low since some of the impulses are not thus perceptible.⁵¹ On the other hand, elaborate apparatus necessitating the application of a mask to the infant's face, and the measurement of expired air in a spirometer, may easily interfere with normal processes and result in the registration, of a falsely rapid rate. Thus, with apparatus of this type, however carefully and ingeniously balanced, Dohrn,⁵⁰ von Recklinghausen,⁵² and Eckstein and Rominger⁵³ recorded average rates, respectively, of 62, 62, and 62.5 respirations per minute, figures which are probably too high but which agree so well with one another that they still persist in some works of reference. Probably the most nearly correct determinations have been made by

Murphy and Thorpe,⁵⁴ Deming and Washburn,⁵⁵ and Deming and Hanner.⁵⁶ All of these workers placed infants in a body plethysmograph, an air-tight chamber from which the head protruded through a rubber collar carefully applied to the neck. After a certain period of acclimatization to such circumstances the subjects could sleep or rest quietly with no mask, tubing, or other obstruction to the flow of air from the mouth and nose. The interior of the

TABLE 4

RATE AND VOLUME OF RESPIRATION

(Studies from 18 infants selected from the data of Deming and Hanner⁵⁶)

Age in Days	Rate per Minute		Tidal Air per Breath		Respiratory Volume per Minute	
	Range	Average	Range (cc.)	Average (cc.)	Range (cc.)	Average (cc.)
1 (day of birth)	27-82	41	10-27	19	225-1187	734
2	27-82	43	12-25	18	436-1704	757
3	23-66	40	12-30	19	465-1003	817
5	25-70	41	15-26	19	550-1452	776
7	28-59	44	14-23	19	490-1222	943
9	32-80	49	13-27	21	681-1663	989
11	32-72	46	25-25*	25*	806-1774	1144*

* Only two samples.

chamber was connected to a delicate spirometer, usually of the Krogh type, so that every respiratory movement of the infant was recorded by the displacement of the air surrounding its body. In 50 infants, most of whom were under two days of age, Murphy and Thorpe⁵⁴ obtained an average respiratory rate of 43 per minute, while in 18 infants from birth to 11 days old, Deming and Hanner⁵⁶ obtained an average of 44. One would be inclined to adopt this as certainly a very close approximation to the physiological truth had not the author of a still more recent study⁴⁶ published an average rate of 60 per minute for 19 infants. It is suggested that 43 or 45 be accepted as the proper figure until further evidence establishing the more rapid rate is forthcoming. The observations of Deming and Hanner,⁵⁶ although not drawn from a very large group of subjects, may be presented as a useful series of measurements. (Tables 4 and 5.)

All workers have noted the wide variability of respiratory rate in the newborn. Thus, Murphy and Thorpe report extremes of 24 and

116 breaths a minute in sleeping infants, and Deming and Hanner found figures as far apart as 16 and 93. Restlessness always brings about irregularity, while crying obviously tends to slow and deepen breathing. It is important that the respiratory rate and regularity never be interpreted as indicative of pathology in neonatal life without consideration of these wide normal variations.

Shaw and Hopkins⁵⁷ used the body plethysmograph method also to record the respiratory activity of 9 premature infants weighing from 1077 to 2300 grams (av. 1660 grams). These showed higher rates than the full-term infants studied by the same method, with extremes of 31 and 114 per minute and a general average of 58.

TABLE 5

MAXIMUM RESPIRATORY VOLUME OBSERVED DURING THE FIRST TEN DAYS OF LIFE
IN 18 INFANTS (DEMING AND HANNER⁵⁶)

Age	Maximum volume of 1 respiration (crying)
1 (day of birth)	160 cc.
2	171 cc.
3	136 cc.
4	181 cc.
6	147 cc.
8	173 cc.
10	149 cc.

Again, when a premature infant was studied by Eckstein and Rominger⁵³ with the mask technique, the mean rate of respiration was as high as 65.

No very consistent trends of the respiratory rate have been observed with the passage of the first two weeks of life, though Table 4 shows a slight increase from the first to the eleventh day. Vogt,⁵⁸ whose general figures may be slightly too low, noted a rise from an average of 32.6 on the first to one of 43.7 on the eighth day. Murphy and Thorpe were impressed by the fact that the minute volume increased in early infancy not so much from a larger number of breaths per minute as from an increase in the depth of breathing as is roughly true also for the figures in Table 4.

As to the volume of respiration (or tidal air) one finds somewhat less disagreement among observers than regarding respiratory rate. Suspicion of mechanical errors is aroused by the observations of Dohrn on 100 infants whose average volume of respiration during the first ten days of life was given as 43 cc., but this figure has unfortunately been accepted in reference works on the newborn. Ac-

tually the more recent work with the plethysmograph has indicated values of from 16 to 20 cc. as the average tidal air during the first week. There is again much variation in the individual infant, and a considerable increase in depth during crying—a maximum volume of 160 cc. having been observed on the first day and as much as 181 cc. on the fourth. It has been suggested⁵⁶ that these volumes must approach the vital capacity for the infants studied. Even though the vital capacity be no greater than this, the residual

TABLE 6
RESPIRATION AS RELATED TO BODY WEIGHT

	Rate	Tidal Air	Min. Vol.	Vit. Cap.
Mature Newborn (1/20 adult weight)	44	19.0 cc.	838 cc.	±170 cc.
Premature Newborn (1/40 adult weight)	58	12.3 cc.	713 cc.	
Adult	18	450.0 cc.	7,100 cc.	3,500 cc.
Mature Newborn Values ×20		380.0 cc.	16,760 cc.	3,400 cc.
Premature Newborn Values ×40		492.0 cc.	28,520 cc.	

air must be considerable in ordinary breathing, and not so meager as has been assumed from roentgenological observations. The maximum depth of inspiration presented in Table 5 does not show a consistent increase during the passage of the first ten days of life, though it will be noted from the preceding table that the general average depth of quiet breathing becomes larger. The tidal air of the premature is, of course, less than that of the full-term infant. Shaw and Hopkins report an average of 12.3 cc. for nine infants weighing from 1.08 to 2.3 Kg. and a measurement of only 4.5 cc. for an infant of 1077 grams, a rather striking illustration of the miniature character of premature human existence.

When the purely quantitative aspects of premature and neonatal breathing are compared with those of the adult on the basis of body size in terms of weight, the results are somewhat interesting. The 3½ pound premature is about one-fortieth the weight of an adult, the mature infant perhaps one-twentieth of the same standard. Therefore the factors 40 and 20 have been used in Table 6 to convert the respective neonatal respiratory performances to figures which may be contrasted with the breathing of the adult.

The comparison is probably an exceedingly crude one but obviously indicates that, in proportion to weight and with a probable vital capacity of the same proportionate order as that of the adult,

the newborn infant has a minute volume about two and one-half times as great as that of the adult, which is achieved by much more rapid and a little less deep respiration. In proportion to its weight the premature infant has a somewhat greater tidal air and a much greater minute volume, the result of a still more rapid rate of respiration. Thus, when the three organisms are reduced to standard size, the breathing of the ordinary infant moves more than twice, and that of the premature about four times, the adult minute volume of air.

It may be permissible to make comparisons on the basis of weight between the infant and the adult regarding tidal air and vital capacity, and indeed the data do show that certain of the compared values are actually quite similar. However, as has been known from the time of Rubner,⁵⁹ the minute volume is not a function of body size but (roughly) of body surface, and this applies not only in members of the same but of differing species. Thus, expressed in terms of cc./kg. body weight/hour, the oxygen consumption of a mouse is 2500 while that of a man is 200,⁴⁴ but per square meter of body surface per hour the oxygen consumption is between 7 and 9 liters in both organisms. If the hypothetical human beings tabulated above be measured in terms of body surface, the following results appear:*

TABLE 7
RESPIRATION AS RELATED TO BODY SURFACE

Relative Weights	Subject	Surface Area	Relative Surface Area	
100%	70 kg. Man	1.745 sq. m.	100%	
5%	3.5 kg. Newborn infant	0.236 sq. m.	13.5%	
2.5%	1.75 kg. Premature infant	0.154 sq. m.	8.8%	
Respiratory performances reduced to standard surface area:				
	Rate	Tidal Air	Min. Vol.	Vit. Cap.
Adult	(18/min.)	450 cc.	8,100 cc.	3,500 cc.
Newborn value	(44/min.)	140 cc.	6,200 cc.	1,180 cc.
0.135				
Premature value	(58/min.)	140 cc.	8,060 cc.	
0.088				

* A more extensive table is given on p. 142.

Thus the minute volume of respiration in newborn and premature infants *on the basis of surface area*, comes quite close to the adult performance.* Nevertheless, this is accomplished at the expense of vastly greater respiratory effort, since the labor of breathing 44 or 58 times a minute to meet the demands of an inordinate body surface is obviously more than that of 16 breaths per minute. This penalty of size is of course not one which is remitted in a short period of adjustment after birth. It gradually declines with the passage of infancy and childhood.

The literature presents numerous kymograph tracings showing the rhythms of respiration in the very young, and among them various forms recur so commonly as to permit a certain amount of grouping or classification. Deming and Washburn⁵⁵ have listed the following patterns observed among normal resting infants: A) *Regular*, in which inspiration and expiration are of equal length, with no pause after expiration; B) *Cogwheel* (observed least frequently), in which expiration is prolonged, often slightly jerky, and followed by a pause; C) *Periodic*, with or without actual apnea between the periods. The character of these respiratory patterns appears in the tracings reproduced in Figure 13 from Deming and Washburn. No one of these types seemed to these authors to be more efficient than the others as indicated by the minute volume (though this was slightly diminished during cogwheel breathing), nor was any single rhythm consistently exhibited by an individual infant. Periodic respiration, in their study, tended to be a comparatively late phenomenon in neonatal life, whereas cogwheel breathing occurred earlier. Murphy and Thorpe observed periodic or Cheyne-Stokes breathing as an uncommon phenomenon usually appearing at the beginning of sleep. In general, slowing of the respiratory rate seems to occur in sleeping infants with associated increase in depth; the minute volume has been observed to decrease in sleep, usually because of slower rather than shallower excursions.⁵⁵

Alterations of regular rhythm appear often enough in the respiration of seemingly normal infants so that they should perhaps not cause any apprehension. Nevertheless, the frequency with which they do occur, particularly in prematures, may suggest something of the physiologic stresses of the newborn period. Whereas some form of periodicity appeared in less than a third of the tracings from a large series⁵⁶ of sleeping full-term infants, several authors have stated that periodicity is the characteristic respiratory pattern

* The very small vital capacity figure for the newborn when compared with the adult on the basis of relative surface areas (1180 cc. as against 3500 cc.) disproves Dreyer's belief that the vital capacity is a function of body surface.⁶⁰

of the premature.⁶¹⁻⁶³ Salmi and Vuori⁶¹ present tables to show that in only two of fourteen prematures aged from birth to 45 days was periodic breathing of the Cheyne-Stokes type never noted. Breathing of this type in adults is usually associated with enfeebled func-

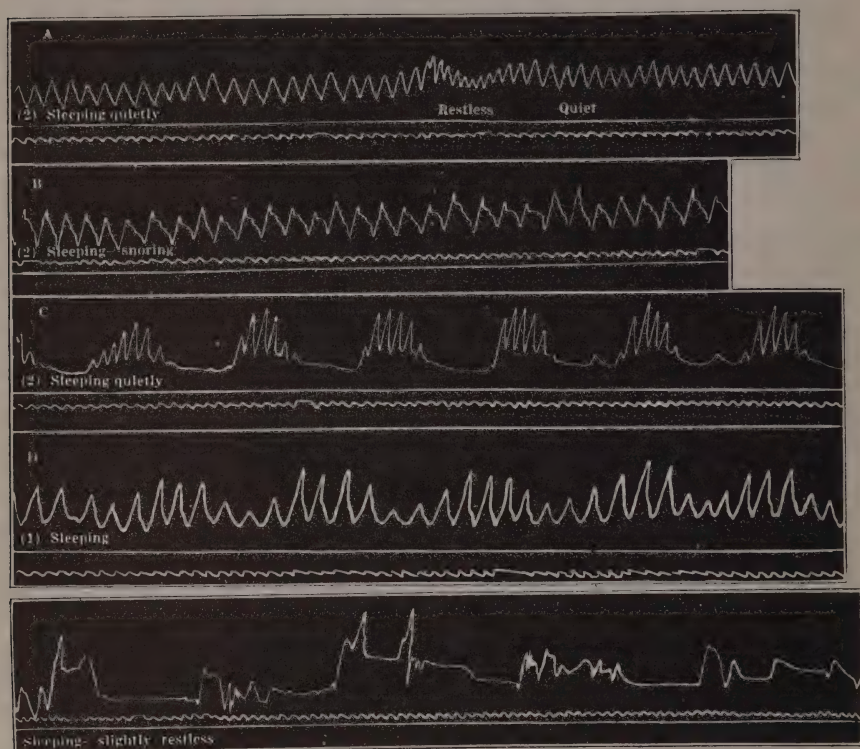


FIGURE 13

Tracings of common respiratory rhythms of normal full-term infants:

- A. *Regular*—Infant aged 12 days.
 - B. *Cog-wheel expiration*—Age 5 weeks.
 - C. *Extremely periodic*—Age 25 days.
 - D. *Moderately periodic*—Age 4 weeks.
 - At bottom—*Bizarre irregularity*—Age 4 days.
- (Deming, Washburn, *Am. J. Dis. Child.*, 49: 108, 1935.)

tioning of the respiratory centers, and this may be its explanation in the premature infant. Schmidt believes it to be always the mark of anoxia of the brain, and suggests that in the newborn infant some degree of birth injury and congenital imperfection of the respiratory neurones may also play a role. Two not very easily reconciled experimental observations have been put forth on this

subject. One is the partially successful attempt of R  ih   and Salmi⁶² to show that periodicity can result from the excess hemoglobin often present in early prematurity. These authors tried with some success to produce periodic respiration by artificially increasing the hemoglobin content in the blood of young rabbits. The second observation, and the one which seems somewhat more acceptable, is that of Wilson and his colleagues⁶³ who found that the Cheyne-Stokes type of breathing in the resting premature baby could be altered to a regular rhythm by supplying an atmosphere of increased oxygen to the infant. The periodic breathing thus supplanted had occurred in the absence of any cyanosis. Coupled with the measurements of oxygen unsaturation and the deficiency in carbonic anhydrase mentioned above (see page 28) for the apparently normal non-cyanotic infant, Wilson's observations strongly suggest that periodic respiration in the premature and, by analogy, in the mature infant, may be "normal" to that organism but nevertheless a sign of life maintained somewhat precariously when judged by adult standards.

Still other types of respiration are occasionally seen in infants very early in life although their more than transient presence is strongly suggestive of irreversible damage to the nervous control of breathing. These are panting and gasping or hiccoughing efforts, so unsuited to efficient pulmonary respiration and so often combined with characteristic movements of the lower jaw and tongue that Peiper⁶⁴ has explained them as reversion to more primitive forms of respiratory center activity. He suggests that, as the control mechanism deteriorates, lower and developmentally earlier "centers" take over its function, bringing about a sort of breathing which suggests the swallowing respiration of *amphibia* as described by Krogh.⁴⁴ The matter is worthy of remark as illustrating the relative rather than absolute nature of satisfactory breathing in newborn life. Somewhere between an inadequate pattern of primitive gasping and swallowing, and the finely balanced control characteristic of later extra-uterine life, is located the newborn infant's usual respiratory performance.

CLINICAL SUMMARY

Although the most important stimulus for the onset of breathing at birth appears to be the sudden anoxia resulting from interruption of the oxygen supply received from the mother, a sufficiently prolonged period of anoxia may disturb the mechanisms involved so that they are no longer able to act properly. These mechanisms, among which the aortic and carotid chemo-receptors are perhaps

more important than the medullary "center," may then fail to function at all, or may function only to the extent of producing inefficient and irregular gasping. Obviously such events are more likely to occur after protracted, difficult, or traumatic deliveries, and their effects may be increased by the employment of an excessive amount of anesthesia or narcosis.

The newborn infant possesses an unexplained but only relative immunity to anoxic damage, for it will survive a longer interval of suspended respiration than will the older subject. Just how long a period may be tolerated cannot be stated but 15 minutes is probably within the extreme limit. Nevertheless, the longer the anoxia, the more the integrity of the central nervous system is jeopardized, and the greater the probability that the infant may survive only as a permanently damaged individual. During periods of apnea or of inefficient respiration, the infant receives some benefit from the oxygen in swallowed air, and may also absorb a small quantity through the skin so that there is more than one reason for keeping the partially asphyxiated infant in a high oxygen environment.

A certain amount of amniotic fluid may be present in the respiratory tract of the normally delivered infant, and, of itself, need not be an important help or hindrance to the development and expansion of the lungs. However, inflation of the lungs does require a greater inspiratory effort at birth than in normal breathing thereafter, though the force required is seldom beyond the muscular capacity of the normal infant even though prematurely born. A negative pressure equal to the weight of 30 or more cm. of water may be necessary for expansion; pressures of this degree must be within the range of mechanical resuscitating devices if they are to be successfully used. The infant's lung will probably withstand such forces without significant alveolar rupture. Because of the effort and time required for the transformation of the moist and collapsed fetal lung to the buoyant expansion of normal extra-uterine life, some degree of persistent primary atelectasis may be roentgenologically demonstrable for more than a week after birth in quite normal infants. Its presence does not necessarily signify a pathological state, nor should atelectasis, even of large degree, be accepted as a primary cause for co-existent symptoms until a search has been made for more fundamental causes underlying the atelectasis.

Breathing is essentially a diaphragmatic and abdominal activity in neonatal life, the thorax offering little more than a relatively fixed chamber in which the diaphragm's descent and ascent induce movement of air. In some newborn infants, and in many prematurely born ones, the thorax is sufficiently yielding so that it may

be unable to withstand the negative pressure of inspiration, and collapses inwardly with each breath. This, of course, decreases the efficiency of respiration.

The rate and the depth of breathing in the normal newborn, though extremely variable, are such as to move much more air in and out of the lungs—in proportion to body weight—than is the case in adults. This is a result of metabolic considerations associated with body size and surface. It is brought about more by a disproportionate frequency of breathing than by an excessive amount of air per breath. The average respiratory rate is about 44 per minute, with extremes under normal resting circumstances of 20 and 100. All of these figures tend to be higher in premature infants. The tidal air of the average breath is from 16 to 20 cc., smaller values occurring in prematures. A tidal air volume as great as 180 cc. has been noted in the deep inspirations of the crying infant.

Irregularity or regular periodicity of respiration occurs frequently in the neonatal period, and almost characteristically in prematurely born infants. Even when such subjects display no dyspnea or cyanosis, the change from a periodic to a normal respiratory rhythm which follows an increased oxygen supply indicates that these peculiarities signify a marginal status of anoxia. While there are reasons for evaluating clinical observations in newborn patients with some regard to the respiratory features peculiar to this stage of life, certain of these features may arise from a lack of oxygen which had best be prevented.

BIBLIOGRAPHY

1. SCHMIDT, C. F.: in Macleod's Physiology in Modern Medicine, 9th ed. (P. Bard, ed.), St. Louis, C. V. Mosby, 1941.
2. EASTMAN, N. J.: Foetal blood studies; chemical nature of asphyxia neonatorum and its bearing on certain practical problems, *Bull. Johns Hopkins Hosp.* 50: 39, 1932.
3. HEYMANS, C., and BOUCKAERT, J. J.: Les chémorécepteurs du sinus carotidien, *Ergebn. d. Physiol.* 41: 28, 1939.
4. SCHMIDT, C. F., and COMROE, J. H., JR.: Functions of carotid and aortic bodies, *Physiol. Rev.* 20: 115, 1940.
5. COMROE, J. H., JR.: Location and function of chemoreceptors of aorta. *Am. J. Physiol.* 127: 176, 1939.
6. DUMKE, P. R., SCHMIDT, C. F., and CHIODI, H.: Part played by carotid body reflexes in respiratory response of dog to anoxemia with and without simultaneous hypercapnia, *Am. J. Physiol.* 133: 1, 1941.
7. WILSON, R. A., TORREY, M. A., and JOHNSON, K. S.: Initiation of respiration in asphyxia neonatorum; clinical and experimental study incorporating fetal blood analysis, *Surg., Gynec. & Obst.* 65: 601, 1937.

8. GOODMAN, L. S., and GILMAN, A.: *The Pharmacological Basis of Therapeutics*, New York, Macmillan, 1941.
9. FELDMAN, W. M.: *Principles of Ante-Natal and Post-Natal Child Physiology*, Pure and Applied, London, Longmans, Green & Co., 1920.
10. BERT, PAUL: *Leçons sur la physiologie comparée de la respiration* . . . Paris, J. B. Baillière & Fils, 1870.
11. REISS, M., and HAUROWITZ, F.: Über das Verhalten junger und alter Tiere bei Erstickung, *Klin. Wchnschr.* 8: 743, 1929.
12. BORGARD, W., and HOFFMANN, F.: Über das Verhalten von neugeborenen Tieren bei Sauerstoffmangel, *Arch. f. Gynäk.* 168: 873, 1939.
13. HIMWICH, H. E., ALEXANDER, F. A. D., and FAZEKAS, J. F., Tolerance of the newborn to hypoxia and anoxia, *Am. J. Physiol.* 133: 327, 1941.
14. SELLE, W. A., and WITTEN, T. A., Survival of respiratory (gaspings) mechanism in young animals subjected to anoxia, *Proc. Soc. Exper. Biol. & Med.* 47: 495, 1941. Also *Am. J. Physiol.* 133: 441, 1941.
15. TYLER, D. B., and VAN HARREVELD, A.: Respiration of developing brain, *Am. J. Physiol.* 136: 600, 1942.
16. HIMWICH, H. E., FAZEKAS, J. F. and ALEXANDER, F. A. D.: Effects of cyanide and iodoacetate on survival period of infant rats, *Proc. Soc. Exper. Biol. & Med.* 46: 553, 1941.
17. BRINKMAN, R., and JONXIS, J. H. P.: Estimation of arterial unsaturation, especially in pediatric conditions, *Acta Med. Scandinav.* 94: 453, 1938.
18. SMITH, C. A., and KAPLAN, E.: Adjustment of blood oxygen levels in neonatal life, *Am. J. Dis. Child.* 64: 843, 1942.
19. WINDLE, W. F., and BECKER, R. F.: Asphyxia neonatorum; experimental study in guinea pig, *Am. J. Obst. & Gynec.* 45: 183, 1943.
20. SCHREIBER, F.: Neurologic sequelae of paranatal asphyxia, *J. Pediat.* 16: 297, 1940.
21. REIFFERSCHIED, K.: Über intrauterine Atembewegungen des Fötus, *Deutsche med. Wchnschr.* 37: 877, 1911.
22. COHNSTEIN, J., and ZUNTZ, N.: Weitere Untersuchungen zur Physiologie des Säugethier-Fötus, *Arch. f. d. ges. Physiol.* 42: 342, 1888.
23. WALZ, W.: Über die Bedeutung der intrauterinen Atembewegungen Monatschr. f. Geburtsh. u. Gynäk. 60: 331, 1922.
24. SCHMITT, W.: Über die Bedeutung der intrauterinen Atembewegungen beim Fötus. *Ztschr. f. Geburtsh. u. Gynäk.* 90: 559, 1927.
25. SNYDER, F. F., and ROSENFELD, M.: Fetal respiration in relation to atelectasis and intrauterine pneumonia, *Am. J. Obst. & Gynec.* 36: 363, 1938.
26. SHOCK, N. W.: Fetal aspiration of amniotic fluid, *Am. J. Physiol.* 134: 769, 1941.
27. WHITEHEAD, W. H., WINDLE, W. F., and BECKER, R. F.: Changes in lung structure during aspiration of amniotic fluid and during air-breathing at birth, *Anat. Rec.* 83: 255, 1942.
28. POTTER, E. L., and BOHLENDER, G. P.: Intrauterine respiration in relation to development of fetal lung, with report of 2 unusual anomalies of respiratory system, *Am. J. Obst. & Gynec.* 42: 14, 1941.

29. FARBER, S., and SWEET, L. K.: Amniotic sac contents in lungs of infants, *Am. J. Dis. Child.* 42: 1372, 1931.
30. SZLÁVIK, F.: Über Lungenveränderungen bei Neugeborenen mit besonderer Berücksichtigung der Fruchtwasseraspiration, *Beitr. z. path. Anat. u. z. allg. Path.* 89: 40, 1932.
31. CAMERER, J.: Beiträge zur Frage der Fruchtwasseraspiration, *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 29: 333, 1938.
32. SMITH, C. A., and CHISHOLM, T. C.: Intrapulmonary pressures in newborn infant, *J. Pediat.* 20: 338, 1942.
33. HERMANN, L.: Über den atelectatischen Zustand der Lungen und dessen Aufhören bei der Geburt, *Arch. f. d. ges. Physiol.* 20: 365, 1879-80.
34. WILSON, J. L., and FARBER, S.: Pathogenesis of atelectasis of newborn, *Am. J. Dis. Child.* 46: 590, 1933.
35. UNGAR, E.: Zur Lehre von der Lungenatelektase, *Jahrb. f. Kinderh.* 69: 505, 1909.
36. FARBER, S., and WILSON, J. L.: Atelectasis of newborn; study and critical review, *Am. J. Dis. Child.* 46: 572, 1933.
37. PEISER, J.: Über Lungenatelektase: *Jahrb. f. Kinderh.* 67: 589, 1908.
38. WEYMULLER, C. A., BELL, A. L. L., and KRAHULIK, L.: Roentgenographic changes in thorax of normal newborn babies; daily roentgenographic study of 25 normal babies during first 14 days of life, *Am. J. Dis. Child.* 35: 837, 1928.
39. FARRELL, J. T.: Roentgen appearance of chest of new-born infant, *Am. J. Roentgenol.* 24: 140, 1930.
40. SOLIS-COHEN, L., and BRUCK, S.: Roentgen examination of chest of 500 newborn infants for pathology other than enlarged thymus, *Radiology* 23: 173, 1934.
41. DUNHAM, E. C., and D'AMICO, M.: Roentgenographic study of thoraces of newborn infants, *Yale J. Biol. & Med.* 6: 385, 1934.
42. DILLON, J. G.: Respiratory function of digestive tract as basis of roentgenographic life test, *Am. J. Roentgenol.* 48: 613, 1942.
43. KROGH, A.: Experiments on the cutaneous respiration of vertebrate animals, *Skandinav. Arch. f. Physiol.* 16: 348, 1904.
44. KROGH, A.: Comparative Physiology of Respiratory Mechanisms, Philadelphia, University of Pennsylvania Press, 1941.
45. SCAMMON, R. E., and RUCKER, W. H.: Changes in the form and dimensions of the chest at birth and in the neonatal period, *Am. J. Dis. Child.* 21: 552, 1921.
46. BAUER, A. R.: Respiration in newborn infants, *Am. J. Dis. Child.* 60: 1342, 1940.
47. SCHERER, F.: Die Respiration des Neugeborenen und Säuglings, *Jahrb. f. Kinderh., N. F.* 43: 471, 1896.
48. PEIPER, A.: Die Atmung des Neugeborenen, *Jahresk. f. ärztl. Fortbild.* 24: 21, 1933.
49. GREGOR, K.: Untersuchungen über die Athmungsgrösse des Kindes, *Archiv. f. Anat. u. Physiol. (Physiol. Abt.) Supp.* p. 59, 1902.
50. DOHRN, R.: Über die Grösse des respiratorischen Luftwechsels in den ersten Lebenstagen, *Ztschr. f. Geburts. u. Gynäk.* 32: 25, 1895.
51. FUHRY, E.: Über die Atemfrequenz der Frühgeburten, *Kinderärztl. Praxis* 6: 258, 1935.

52. VON RECKLINGHAUSEN, H.: Über die Athmungsgrösse des Neugeborenen, *Arch. f. d. ges. Physiol.* 62: 451, 1896.
53. ECKSTEIN, A., and ROMINGER, E.: Zur Physiologie und Pathologie der Atmung. 1. Die Atmung des Säuglings, *Ztschr. f. Kinderh.* 28: 1, 1921.
54. MURPHY, D. P., and THORPE, E. S.: Breathing measurements on normal newborn infants, *J. Clin. Investigation* 10: 545, 1931.
55. DEMING, J., and WASHBURN, A. H.: Respiration in infancy; method of studying rates, volume, and character of respiration, *Am. J. Dis. Child.* 49: 108, 1935.
56. DEMING, J., and HANNER, J. P.: Respiration in infancy; study of rate, volume, and character of respiration in healthy infants during neonatal period, *Am. J. Dis. Child.* 51: 823, 1936.
57. SHAW, L. A. K., and HOPKINS, F. R.: Respiration of premature infants, *Am. J. Dis. Child.* 42: 335, 1931.
58. VOGT, H.: Die Atemzahl des gesunden Kindes, *Monatschr. f. Kinderh.* 42: 460, 1929.
59. RUBNER, M.: Über den Einfluss der Körpergrösse auf Stoff- und Kraftwechsel, *Ztschr. f. Biol.* 1: 536, 1883.
60. DREYER, G.: The normal vital capacity in man and its relation to the size of the body . . . *Lancet* 2: 227, 1919.
61. SALMI, T., and VUORI, E. E.: Untersuchungen über den Atmungstypus der Frühgeburten, *Acta Paediat.* 9: 432, 1930.
62. RÄIHÄ, C. E., and SALMI, T.: Über die periodische Atmung der Frühgeborenen, *Acta paediat.* 15: 198, 1934.
63. WILSON, J. L., LONG, S. B., and HOWARD, P.: Respiration of premature infants; response to variations of oxygen and to increased carbon dioxide in inspired air, *Am. J. Dis. Child.* 63: 1080, 1942.
64. (a) PEIPER, A.: Der Zerfall des Atemzentrums, *Monatschr. f. Kinderh.* 47: 189, 1930.
(b) PEIPER, A.: Die Atembewegungen des Unterkiefers, *Jahrb. f. Kinderh.* 139: 117, 1933.

Chapter IV

THE CIRCULATORY SYSTEM

Section 1 . . .	The Fetal Circulation and Its Alterations at Birth
Section 2 . . .	The Umbilical Vessels at Birth
Section 3 . . .	The Fetal and Neonatal Blood Volume
Section 4 . . .	The Heart and Vascular System
Section 5 . . .	The Dynamics of Circulation
Section 6 . . .	Fetal and Neonatal Blood Pressures
Section 7 . . .	Clinical Summary

THE FETAL CIRCULATION AND ITS ALTERATIONS AT BIRTH

A DETAILED DESCRIPTION of embryological and fetal circulatory mechanisms would be out of place in this chapter and is, fortunately, unnecessary since the subject has been reviewed so recently and so well in Windle's book on the fetus.¹ Nevertheless, some of the prenatal picture must be presented, for the newborn infant has lived so long as embryo and fetus and has undergone so important an alteration by relinquishing the circulatory organization of fetal life, that its newly acquired circulation cannot be discussed without reference to the abandoned one. Since the matter has its controversial aspects, it may be better to use these conflicts as subjects for discussion rather than to deny that controversy exists or to increase it by taking one side or another.

The principal question about the fetal circulation concerns the degree of separation or of mixing which occurs between the two streams of blood coming into the fetal right auricle. In its normal extra-uterine function, this chamber collects the streams of more or less similar venous blood from the superior and inferior *venae cavae*, and passes the resultant mixture on to the right ventricle for aeration in the lungs. There is thus but one means of outflow from the right auricle, and although there are two channels of inflow it is probable that they carry blood of roughly identical composition. In the fetus, on the other hand, there are two channels of outflow; blood passes from the right auricle not only into the right ventricle but also, by way of the *foramen ovale*, into the left auricle

and ventricle as well. In fetal life, moreover, the two streams coming into the right ventricle are not at all similar but are of very different composition, that from the *inferior vena cava* containing

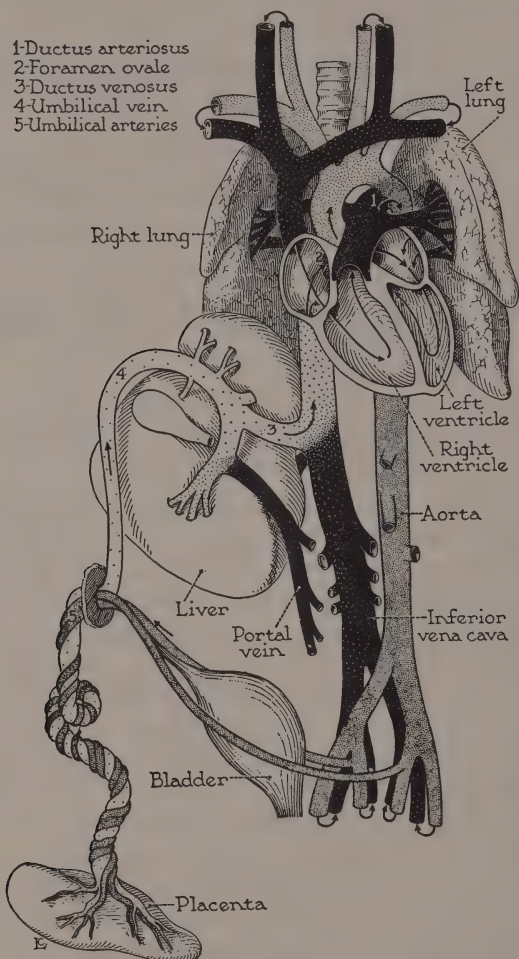


FIGURE 14

The fetal circulation, indicating the course of blood and the pattern of reduction in its oxygen content (from light to dark shading) if some crossing of streams occurs in the right auricle. (Windle, *Physiology of the Fetus*, Philadelphia, W. B. Saunders Company, 1940.)

blood from the placenta, and carrying oxygen as described in a preceding section. When this blood leaves the placenta it may have an oxygen saturation to perhaps 60 to 80 per cent of its capacity.

Although some decrease in the oxygen level must occur by admixture with venous blood returning from the lower part of the fetal body in the inferior *cava*, when the confluent stream from umbilical vein and inferior *cava* reaches the auricle it consists of the most oxygenated blood coming to the heart. On the other hand, there is no doubt that the *superior vena cava* brings poorly oxygenated venous blood from the fetal head and arms.

The early notion that the stream from below retained its relatively arterial character by crossing the flow of more venous blood coming down into the right auricle from the superior *cava* was challenged by Pohlman,² on the basis of his finding that particulate matter injected into the umbilical vein of living (pig) fetuses could be recovered almost immediately in equal concentrations from both right and left ventricles. This could only be possible if the current from the umbilical vein were equally distributed to both ventricles or if it suffered complete admixture with all other blood coming into the auricles. The oxygenated blood coming to the heart in the umbilical vein of such a circulation must lose its identity as an individual stream in the process of raising the general level of oxygenation in the blood of both ventricles. Actually, Kellogg³ found the amounts of oxygen to be almost equal in blood samples obtained simultaneously from the right and left ventricles of dog fetuses, which was strong evidence that a mixture of physiological as well as of artificial substances occurs. On the other hand, Huggett,⁴ and later Barcroft and his colleagues^{5,6} found in the goat and sheep that individual samples representing the output of the two ventricles of a fetus (i.e., blood from the carotid artery as compared with blood from the umbilical artery) showed quite dissimilar oxygen contents, even though the former should represent the output of the left ventricle and the latter (somewhat less definitely) that of the right. The differences indicated that a more arterial type of blood came from the left ventricle. This could only happen if such blood coming through the umbilical vein made its way across the right auricle and flowed out to the left heart through the *foramen ovale* without admixture and dilution occurring along that course. An interesting point and one perhaps significant of technical accuracy was that most of these measurements showed considerably higher values for oxygen than appear in the work of Kellogg. In general, the presence of very much oxygen unsaturation in any sample from the fetal circulation suggests interference with the physiological state, through irritation of the tissues or some other artefact introduced by the technique of investigation. Although the results of analyses have certainly not given an un-

equivocal answer to the question of crossing or mixture of the streams, one is thus a little more inclined to accept the work of Barcroft's group. Admittedly the procedures represent investigations upon animals of different species and in no case the human one, but the circulation in all mammals must be fairly similar in this basic respect. We do not know that there is crossing of the streams but we suspect from these data that it occurs.

One cannot put forward a theory to explain a particular aspect of the circulation unless the theory postulated is in harmony with every other aspect. The workers mentioned thus far have sometimes neglected the flow of blood from the fetal lungs into the left heart as a factor to be reckoned with in a consideration of fetal blood currents. The convenient assumption has been made that almost all the blood from the right ventricle avoids the pulmonary vessels by coursing through the *ductus arteriosus* into the aorta. In that case very little blood could come back from the pulmonary circuit to confuse the oxygen analyses by swelling the contents of the left auricle and ventricle and thus encroaching on whatever amount of oxygenated blood the left heart could accept via the *foramen ovale* from the right auricle. This problem of the fetal pulmonary circuit is not only an important part of the somewhat academic question of the fetal circulation as a whole, but also must be taken into account in considering respiration and circulation in the first hours of neonatal life. Is the blood after birth suddenly finding its way through a relatively unused set of pulmonary vessels?

Such a conception has been challenged by Patten,^{7,8} whose work has the great advantage of using human rather than animal material, although it is mostly founded upon anatomical measurements of the chambers of the heart and their walls and orifices. Patten has by these means brought forth evidence which strongly suggests not only that the pulmonary circuit may receive and return a considerable quantity of blood, but also that the *foramen ovale* may afford a considerably smaller functional opening during fetal life than is usually believed. Both these factors would combine to favor admixture of blood streams in the right heart, as well as reduction in the oxygen content of blood reaching the systemic circulation by way of the lungs, the pulmonary veins, and the left auricle and ventricle. This conception also requires that relatively minor re-adjustments be postulated as occurring at birth; the assumption of a sudden major increase in pulmonary circulation becomes unnecessary, nor need it be required that a *ductus arteriosus* large enough to accommodate a major stream must suddenly close when extra-uterine life begins.

Testimony as to Patten's conception can be had by measuring how much of the blood volume is actually in the fetal lungs at any moment. Abel and Windle⁹ have attempted to learn the effect of extra-uterine respiration on the amount of blood in the pulmonary circuit before and after birth, using litters of kittens at term. Some of each litter were allowed to breathe for an hour or so; the others, delivered at the same time, were killed before any breaths could be taken. The amount of blood present in the lungs, as indicated by the amount of iron per unit of tissue, was of the same order in both groups of fetuses; it had not increased with breathing, a finding which supports Patten's conception of a relatively active fetal pulmonary circulation with little change at birth. Since the more blood from the right ventricle is routed through the lungs the less is presented for passage through the *ductus arteriosus*, the theory of a large pulmonary circulation before birth makes rapid and immediate closing of the *ductus* after delivery not absolutely essential. There seems still less actual need for immediate *ductus* closure in view of Patten's finding that the right ventricular wall is more muscular than the left at birth, and the fact that the human electro-cardiogram shows right ventricular preponderance for the first few weeks of life.¹⁰ Moreover, actual measurements of the ventricular pressures in living animal fetuses^{11,12} have shown the pressure in the right side equal to or greater than that in the left. With all these evidences that the right ventricle surpasses the left at birth and after, the *ductus* might certainly be thought to remain patent during a gradual process of closure without any aorta-to-pulmonary reflux of blood through it.

In the fetal sheep the closure of the *ductus* has been observed roentgenologically by Barclay, Barcroft, and others^{13,14} in a series of experiments which deserve to be called beautiful. After injecting radio-opaque material into the umbilical vein, or in some instances into other veins, the authors recorded the alterations in the shadow of the heart and great vessels at birth by means of x-ray cinematography. Within as little as five minutes after delivery the shadow of the *ductus* (at first marked by attaching a piece of fine wire to the vessel itself) showed cessation of blood flow or "functional" closure, an event which could also be proven by the persistence thereafter of a spur-like shadow projecting from the pulmonary trunk, and representing the pulmonary stub of the closed vessel. For comparison with the data of Barcroft and others on the distribution of oxygenated blood by the fetal heart,^{5,6} the authors noted the distribution of radio-opaque contrast material to various vessels before birth. A major portion of the inferior caval stream was thus observed to pass across the right auricle, through the

foramen ovale, and into the left heart. Only a small portion, mingled with blood descending from the superior *cava*, appeared to enter the right ventricle. In all studies in which contrast substances were injected into the jugular vein, the flow from the superior *vena cava* was shown to take the other route through the right auricle and to enter the right ventricle. Not only was crossing of the streams thus demonstrated again, but also at one point the larger part of the right ventricular output was seen to leave the pulmonary trunk by the *ductus*, the lesser part to enter the lungs. Thus do recent observations revert to the early theories of crossed streams and of at least relatively idle pulmonary-circulation before birth.

Very recently Whitehead¹⁵ has constructed an exact model of the right atrium of the fetal cat's heart. Given a stream of liquid entering from the inferior caval orifice under a little greater pressure than that entering from the superior *cava*, a crossing of these currents with only a minor degree of mixing was demonstrated. The performance of a scale model of the same region of the human fetal heart would be interesting to observe. It is still not possible to state with complete certainty of the human fetus that "umbilical vein blood traverses the right atrium where little or no admixture with the superior caval stream takes place"¹⁶ but by analogy with animal physiology, the correctness of this conception seems very probable.

There is no doubt that the *ductus arteriosus* is a vessel of not inconsiderable size at the end of fetal life, no matter how much blood flows through it. Patten⁸ computes its cross section area in the human fetus at term as 15.2 sq. mm., which may be compared with a cross section area of 28.3 sq. mm. for the orifice of the ascending aorta. There seems to be little doubt that this vessel closes, at least "functionally," fairly soon after birth, and the roentgenologic evidence mentioned above shows that in the animal fetus this takes place as soon as four minutes after ligation of the cord. Should it fail to resist the passage of blood by the time the left ventricular pressure becomes greater than the right, a large amount of the aortic content would continue thereafter to escape through the *ductus* into the pulmonary vessels with resultant disturbance in physical signs, blood pressure levels, and bodily development. Exactly how the "functional" closing, or the more leisurely anatomical obliteration which follows it usually within the first three months of life,^{17,18} are brought about is recently becoming better understood, but only after a large amount of labor had more or less obscured the problem. Valve-like folds and projections at the junction of the *ductus* and aorta have in the past been denied^{12,19-21} as regularly as they have been discovered.²²⁻²⁴ Valve mechanisms may of

course occur in some species but not apparently in all. Hamilton, Woodbury, and Woods¹² are certain that a valvular process at least helps in the *ductus* occlusion of the rabbit and dog, but equally certain that no such process guards the human *ductus*. That any external twisting, kinking, or pulling, produced by diaphragmatic, thoracic or pulmonary elements in respiration could possibly close the *ductus* is denied by most authorities including Scammon and Patten. If in the human organism there occurs such a sudden shutting off of *ductus* flow as was roentgenologically observed in the sheep, it is almost certainly the result of contraction by the vessel's own musculature. Windle¹ states simply that the *ductus* closes by sphincter action, and an interesting histological study by v. Hayek²⁵ has described the oblique direction taken by muscle fibers in its wall, a mechanism which would be ideally suited for drawing the vessel walls together. Several authors^{26,27} have noted prodromal proliferative changes in the intima which begin as early as the sixth or seventh month of gestation. Swenson²⁸ denies that this process exists, and it would indeed be difficult to reconcile it with any closing "on schedule" after birth in the premature infant. The weight of evidence seems to testify to such a mechanism, however, and it must be admitted that it would satisfactorily account for the final closure of the *ductus*, without calling for intricate balancing of pressure relationships.

Very recently Kennedy and Clark^{29,30} have developed a technique for direct observation of the *ductus* in the fetal guinea pig which has allowed them to watch the response of the vessel to numerous types of stimuli. In general the largest group of stimuli producing almost immediate closure (by muscular contraction) were those which increased the oxygenation of the fetal blood. Thus, the inflation of the fetal lungs with oxygen was followed promptly by such an effect, but the substitution of nitrogen for oxygen caused the *ductus* to expand until oxygen was again introduced. Exactly similar responses were reported to occur even when all nerve structures which might conceivably serve the *ductus* had been systematically interrupted, so that no neuro-muscular reflex seems to be active in the process.

The *foramen ovale* is provided with an indubitable valve which closes off that orifice in an understandable fashion as soon as the pressure in the left auricle is greater than that in the right. Scammon³¹ states that this occurs with the first respiration but Patten³² argues convincingly that a more gradual process extending perhaps through most of the first month of life is required. The anatomical patency of an orifice thus "functionally" closed is of little immedi-

ate interest, but it may be significant that the *foramen ovale* generally remains open to a probe for somewhat longer than does the *ductus arteriosus*. Christie¹⁸ found that in 25 per cent of infants coming to autopsy at eight weeks the *foramen ovale* was still at least anatomically open, whereas in only 12 per cent was the lumen of the *ductus* not obliterated by this age. There is a suggestion in this of a more active process of proliferative closure in the *ductus arteriosus*. No great interest has been aroused by the closure of the *ductus venosus* since this vessel is only a partial by-pass around the liver and thus modifies the extra-uterine type of circulation only locally. Possibly its patency may be one factor in contributing to icterus neonatorum by providing a route which causes some blood to avoid the liver and thus fail to be cleared of bilirubin.³³ Its occlusion is made against a rather sluggish venous stream and is said to occur functionally³⁴ within the first two weeks after birth. Scammon's table³¹ shows its complete obliteration to be almost always brought about by eight weeks.

However slowly or rapidly these functional or anatomic changes take place in the various channels which characterize the fetal circulation, the matter of final importance is the duration of the adjustment period in terms of the character of blood reaching the tissues. The physical state of the *ductus* or the *foramen ovale* may be disregarded if one can answer the question: How soon after birth do the infant's muscles and brain receive blood highly saturated with oxygen and able to remove carbon dioxide with the efficiency of the usual adult circulation? All of the data available suggest a rather rapid adjustment. In the lamb, Barcroft and his colleagues⁶ have shown that only a few minutes are required for the newborn organism to transform its arterial blood oxygen saturation from 50 per cent or less to 75 or 80 per cent, while 90 per cent is reached within a few hours. Figures 5 and 6, in an earlier chapter, indicate how well the process is managed by the human infant. Although the time varies, only about three hours (and sometimes very much less) seem to be required for transforming a circulation which functions like a fetal circulation to one which—whatever be the anatomical state of its passages—functions like an adult circulation.

THE UMBILICAL VESSELS AT BIRTH

When the great majority of mammals are born no one ligates the umbilical cord, yet it is interesting to observe what attention is devoted at human delivery to this process for which Nature has supposedly made adequate provision, to consider what muscular effort is used in tying the human cord and what devices have been elabo-

rated to guard against an unsatisfactory ligation. Why does the umbilical flow cease in animals? What would happen if the human cord were not tied? It is said that in veterinary obstetrics no important hemorrhage follows the division of the navel cord.³⁵ Two reasons are advanced for this: (1) that pulsation and tension in the umbilical arteries diminish and cease as a result of the onset of respiration, and (2) that the retraction of elastic and muscular tissue in their walls shuts off the torn ends of the vessels. That any change in blood pressure associated with the onset of human respiration alters the pressures within the cord vessels at birth has been convincingly disproven by Haselhorst.³⁶ The average pressure of 70 to 75 mm. Hg cannot be shown to waver significantly with the first breath, so that pulsation in the cord does not cease (in the human infant) because blood is drawn off to the lungs, as was supposed by early theorists.

An interesting feature of fetal physiology is the response of placental vessels to the oxygenation of blood passing through them. Several authors have observed the placental vascular dilatation which accompanies a fall of fetal blood oxygenation below a certain level, and the contraction when the oxygen content rises; Schmitt³⁷ describes numerous perfusion experiments proving this phenomenon. A strikingly similar response takes place in the gill tissues of certain fish and amphibians when the oxygen tension of their water environment is altered.³⁸ A like adjustment of the *ductus arteriosus* has been described above. That the umbilical as well as the placental vessels and the *ductus* respond to the stimuli of increased or decreased oxygenation has been shown by perfusion experiments³⁹ in which buffered Ringer's solution or defibrinated blood was propelled through pieces of human umbilical cord.⁴⁰ The saturation of the perfusing solutions with oxygen caused the vascular walls to contract with vigor, while saturation with carbon dioxide or nitrogen caused dilatation of the vessels. A mechanism is thus available which might not only assist in the exchange of gases between the mother and fetus but would also tend to close off the fetal vessels in the cord as soon as the pulmonary respiration of the newborn organism provided a sufficient increase in oxygen.

Haselhorst³⁶ measured the changes of oxygen content in the three to five minutes during which pulsation continues after a normal delivery. Sixty seconds after pulmonary respiration had begun, the oxygen level in the average umbilical artery blood was found to have risen from 3.1 to 10.3 volumes per cent; umbilical vein blood changed from 8.7 to 12.0 volumes per cent oxygen. Certain figures from the same data indicate that with the passage of further time

a further increase, particularly in the umbilical artery specimen, is to be expected. The changes in the content of the umbilical vein must of course be due to the flow of oxygenated blood from the arteries through the placental vessels and back again toward the fetus. Under the circumstances it appears that the maximum change in the direction of increased oxygenation (and thus the greatest stimulus toward contraction) must occur in the umbilical arteries, which are, indeed, direct continuations of the descending aorta. Their content must thus pass rather rapidly from the debased state of fetal venous blood toward the comparatively elevated one of arterial blood in extra-uterine existence. Confirmatory data from another study of this immediate post-natal adjustment are shown in figure 5. The circumstances are thus particularly well adapted to call forth any specific effect of oxygenation on the walls of the very vessels whose contraction is most imperatively required. Schmitt's perfusion experiments³⁷ showed a beginning contraction of placental vessels at an oxygen threshold of just under 5 volumes per cent; within the first minute after the beginning of breathing the normal infant usually builds up an arterial blood oxygen level of more than twice that amount. One observation which seems at variance with the theory proposed is the weak or absent pulsation usually to be found in the cord vessels of anoxic or asphyxiated babies as compared to the vigorous impulses palpable for a few minutes after the delivery of a crying infant with good muscle tone. However, in circumstances of the former sort the entire peripheral circulation is usually at fault and the umbilical arteries are therefore more or less bloodless.

Haselhorst has shown that there are also effects from the sensitivity of the cord to temperature and to irritation from handling. Decreased environmental temperature is a definite stimulus to contraction of cord vessels. An infant might be expected to bleed to death from all three vessels if the cord were cut across cleanly with a sharp knife at birth and the infant and cord stump were placed in a bath of body temperature. On the other hand, in water of 20° C. or in room air a sharply cut cord will bleed from all vessels for six to ten pulsations, the flow then gradually ceasing.³⁶ Air seems to affect the cord vessels differently from water, the observation having been made that in air the bleeding from the arteries stops sooner than that from the vein. In water, on the other hand, the arteries will continue to ooze longer than the vein. Their severed ends may receive an additional stimulus to contracture in air by direct contact with the oxygen of the atmosphere; air also makes for a rapid decline in temperature by the cooling of evaporation. Any

simple mechanical stimulus such as handling or sponging the cord will cause more or less response, so that at the irritation site a focus of contraction is set up which propagates itself along the cord in either direction. Thus there are two general mechanisms for terminating the flow through the umbilical vessels. One of these is a response to stimuli from within and the other to stimuli from without. Clotting of blood in the vessels may take some time after the flow has ceased; in specimens of cord standing in the laboratory it is often possible to obtain fluid blood from loops of the umbilical vein as long as 15 to 20 minutes after delivery. Certainly clotting has no importance in the cessation of cord circulation.

The human infant might be expected to manage as well as any other newborn mammal without ligature of the cord, particularly if, as with animals, a long remnant were left attached, but tradition, convenience, surgical dispatch, and a certain amount of care against unlikely accident⁴¹ decree that the cord be clamped and severed. The timing of this act is a matter of great variation. Some obstetricians insist upon waiting until the pulsation has ceased, some give the matter little attention, while there are difficult or hazardous circumstances in which delay of any sort may be very unwise for the infant or the mother. In some instances the cord has been clamped at once and the blood contained in the portion distal to the clamp as well as that in the placenta collected and preserved for transfusion or other uses, and at not a few deliveries the cord is clamped with great dispatch so that a representative specimen may be obtained from its vessels for laboratory investigation. It may at once be stated that no proof exists of any serious harm coming to the infant from any of these procedures. On the other hand, the adjustment the infant is prepared to make in the face of such fortuitous blood gains or losses (which will be discussed below) is a striking example of the physiological resiliency of newborn life.

THE FETAL AND NEONATAL BLOOD VOLUME

Much of the distance travelled by the fetal blood as it is circulated *in utero* is through the vessels of the cord and placenta and thus outside the fetal body. As to the percentage of blood which is actually in the placental circulation at any given period of fetal life, there are no data for the human species. Measurements have, however, been made in goats by Elliott, Hall, and Huggett,⁴² the results of which have been interestingly presented by Barcroft, together with a few measurements of his own from sheep fetuses.⁵ The findings indicate the *total* blood volume to be some eight to ten per cent of the combined weight of fetus and placenta fairly

constantly through gestation. However, as birth approaches more of this blood remains in the fetus and less is (at any one moment) in the cord and placenta; one of so many examples of prenatal adjustment toward the manner of postnatal life. Nevertheless, at the time of birth in the goat and sheep, about a quarter of the blood is in the placental circulation. Krafka⁴³ obtained an even larger fraction by measurements of the hemoglobin in the placentas of fetal pigs. The average indicated that about 38 per cent of the total hemoglobin available to the fetus was constantly in the placenta. Almost 30 per cent of the hemoglobin of one human fetus was found by the same author to be in the placental vessels. This specimen was only of five months gestational life, and it may be that the animals studied were also not at term, in which cases these figures would only substantiate Barcroft's statement that in early fetal life a proportionately greater amount of blood is in the placenta than is later the case.

The fact that such a large system of vessels together with more or less of its content is abandoned at birth, is of primary importance in appraising the neonatal circulation. The lungs were once thought to provide a vascular reservoir equal to that lost with the cord and placenta, but even were they completely empty before, their vessels could only accept 10 or, at most, 20 per cent of the total blood volume at birth. Since they are not empty in fetal life, it appears that the alterations of birth can probably allow their acceptance of perhaps an additional five per cent of the total blood volume, whereas the organism has abandoned space for four or five times as much. The actual amount of blood regained by the infant at birth as a result of contractions of the uterus and of the cord vessels can be stated with some exactness. Some fifty years ago both Budin⁴⁴ and Schucking⁴⁵ observed that about 100 cc. of blood flowed from the placenta to the infant after birth, and later measurements⁴⁶⁻⁴⁸ have shown the amount to be sometimes as much as 125 cc. Haselhorst⁴⁷ studied the mechanical forces by which this was supplied to the infant, and found that there was a gain in weight with each immediately postnatal uterine contraction while very strong umbilical vascular pulsations might result in transient decreases in weight. At almost all of 120 deliveries the whole increment had reached the infant by 20 minutes after birth, and often within 10 minutes or less. The process is thus one of rapidly diminishing flow. Since the infant can hardly regain every drop of placental blood it would seem that at the time of birth the placental circuit contains at least 125 to 150 cc. of blood. In the light of the data given below, this can be contrasted with about 310 cc. as the

volume of blood in the body during the first few hours after birth.

It thus seems allowable to offer the tentative conclusion that between one-fourth and one-third of all the human fetal blood is in the placental circuit at the end of gestation. A variable and not inconsequential share of this is in the cord vessels themselves and thus not actually in position for placental exchange at any one moment, but the total amount is so much greater than that later occupying the lungs as to suggest the qualitative inferiority of placental as compared to pulmonary respiration and perhaps also to emphasize the purposes other than respiratory which are served by the placenta.

Measurements of the neonatal blood volume after the immediate adjustments of birth have taken place are grouped in the table below.

TABLE 8

Author	Subjects	Blood Volume/Kg. Body Weight	
		Average	Extremes
Lucas and Dearing ⁴⁹ (1921)	30 infants Age 2½ hrs. to 15 days	147 cc.	107-195 cc.
Lucas and Dearing ⁴⁹ (1921)	11 infants 15 days to 1 yr.	109 cc.	90-126 cc.
Robinow and Hamil- ton ⁵⁰ (1940)	20 infants 1 hr. to 10 days	98.3 cc.	89.6-107 cc.
Brines, Gibson, Kun- kel ⁵¹ (1941)	4 infants 7 to 21 days	*86.0 cc.	*78.4-95.9 cc.
DeMarsh, Windle, Alt ⁴⁸ (1942)	9 infants 15 min. to 3 hrs.	94 cc. (Cord clamped early)	
	16 infants 3 days	96 cc. (Cord clamped early)	
	8 infants 15 min. to 3 hrs.	112 cc. (Cord clamped late)	
	16 infants 3 days	121 cc. (Cord clamped late)	

* (Calculated from authors' data.)

Inasmuch as Robinow and Hamilton, and Brines and his colleagues have not mentioned the retrieving of placental blood in the subjects they studied, DeMarsh, Windle and Alt have performed a real service in offering separate determinations on the basis of this factor, and thus demonstrating that at both ages studied by them the volume was greater if an excess of blood had not been abstracted in the placenta at delivery, and, indeed, that those infants in whom this was prevented showed a somewhat greater augmentation of blood volume in the later measurements as compared to those shortly after birth. Moreover, these authors have demonstrated by hematocrit and plasma volume determinations that the difference in blood volume according to the time the cord is clamped becomes a difference only in red cell mass, the plasma volume being equalized in both groups, by means of what must be a rapid and very nice adjustment of extra-cellular fluid. The effect of this process upon the hemoglobin and iron stores of the infant, as shown in other work by the same investigators, will be discussed later. No other references have been discovered which confirm Lucas and Dearing's demonstration of diminishing blood volume soon after the neonatal period.

Compared with the proportion of blood volume in the adult's body, that of the newborn infant may be about the same or a little higher, depending indeed on the fate of the placental component. It is certainly not often much greater than in the adult. In fact, Brines, Gibson and Kunkel (whose figure happens to be the lowest in the table) and Gibson and Evans⁵² bring evidence to show that per unit of height, of weight, or of body surface, the baby at birth has less blood than does the older child or adult. This, taken with the fact that the heart relinquishes at birth the need for pumping blood through the more distant parts of its former circulation, makes for circumstances which should in many ways favor that organ. A hypothetical infant weighting 3.5 Kg. should have about 350 cc. of blood shortly after birth. If it be assumed that 100 cc. of this amount have been reclaimed from the placental circuit, where perhaps 50 cc. remains behind even after pulsation ceases, then before birth the fetal heart must have had to move 400 cc. of blood, and this through a much longer circuit which included a distance of about 120 cm. to the placenta and back in the average cord alone. After birth it must pump 350 cc., or 87 per cent of its former load, through about 75 per cent of its former vascular bed. The abandoned 25 per cent was a much more distant and difficult area to reach than any of the retained circulatory area. On the

other hand, it must be remembered that before birth blood was driven through a relatively flabby and atonic organism; after birth the infant's tissues assume tone, which would increase resistance. The effects of these various factors may make themselves felt in certain measurable manifestations of the circulation.

THE HEART AND THE VASCULAR SYSTEM

The heart of the infant at birth is developed to a degree compatible with the labor it has been performing, and since that labor is, in some aspects, decreased by the change to extra-uterine life, the size of the heart relative to the body declines during early infancy. Scammon³¹ states that "if the weight of the heart of the newborn be compared to the combined weight of the body and fetal placenta it is found that the relation which the organ bears to the tissues which it supplies with blood is little if any greater than in the adult." The loss of the placenta removes 15 to 20 per cent of the original weight of this system. Mathematical data as to the relative and the absolute weight of the newborn heart are available from three series of measurements,⁵³⁻⁵⁵ though it has been properly pointed out that all are derived from hospital populations and that therefore they may not be absolutely reliable for healthy living infants. The heart weight at birth is 19.5 to 23.6 grams; this remains fairly stationary during the first month, and whereas the body weight is roughly tripled during the first year, the heart weight is only doubled during the same period. The following measurements indicate these relationships.⁵⁵

TABLE 9

RELATIVE WEIGHT OF HEART COMPARED TO WEIGHT OF BODY

Age	Cases	Males Relative Heart Weight, Per Cent	Cases	Females Relative Heart Weight, Per Cent
		$\left(\frac{\text{Heart}}{\text{Body}} \times 100\right)$		$\left(\frac{\text{Heart}}{\text{Body}} \times 100\right)$
Birth	23	0.620	14	0.629
0- 1 mo.	45	0.643	47	0.632
1- 6 mo.	50	0.576	52	0.610
6-12 mo.	34	0.597	32	0.602
15-20 yrs.	23	0.548	13	0.419

The weights of the right and left ventricles⁸⁶ are illustrative of the alterations occurring in the heart function as fetal life changes to extra-uterine life, and as later phases of development occur:

TABLE 10
WEIGHTS OF EACH VENTRICLE

Age	Right Ventricle	Left Ventricle
Birth	6.14 grams	7.15 grams
4-6 months	6.55	12.35
7-12 months	8.04	16.31
3 years	14.98	32.15
11-15 years	34.0	67.1
21-30 years	70.8	125.1

A rapid increase in left ventricular development is apparent. Although in these data the left is from the beginning somewhat larger than the right ventricle, Patten's⁷ measurements have shown that the right ventricle may even be the larger of the two at birth. In any case, the first few months of life are marked by the ascendancy of the systemic circulation; that this process gets under way within the first two weeks is shown by some figures collected by Brock:⁸⁶

TABLE 11
WEIGHT OF RIGHT HEART IN PER CENT OF WEIGHT OF LEFT

Age	Observer	
	W. Mueller	Wideroe
Birth	83.3%	109.0%
2 weeks	71.6	88.5
4 weeks	63.5	72.0
3 months	55.3	62.5

No actual decrease in the right heart is part of this process, but the left side grows rapidly, increasing (according to Scammon³¹) more in thickness of muscle walls than in general expansion.

The heart of the newborn infant has certain peculiarities when examined roentgenographically. As would be expected, the relationship of cardiac to thoracic diameter does not follow the proportions characteristic of later life. Whereas in the roentgenogram of the child's or adult's thorax, the former diameter is normally not more than one-half the latter, it is common to find films of neonatal

infants showing the heart considerably larger than this, so that the *mean* cardio-thoracic ratio in the first three weeks of life has been found by Bakwin and Bakwin⁵⁶ to be 0.55, as compared with the *upper limit* of 0.5 considered normal for older subjects. Since the size of the thorax is subject to such variability in the newborn period it may be wiser to use an absolute measurement of normal heart size rather than a ratio to determine normality or abnormality, and thus to consider any newborn infant's heart to be abnormal if its shadow is wider than 5.5 cm. in a six foot film. It is obvious that any enlargement of the heart demonstrable roentgenographically during the neonatal period is of especial clinical significance, particularly if it be progressive, for this is a time at which the heart should not grow and may normally be decreasing in size. The roentgenogram in the early days of life also shows a heart shadow which tends to vary greatly in size and shape with the position of the patient and particularly—as shown in Figs. 7-12—with the phase of respiration. This calls for extra care in clinical interpretation. One gets also an impression of roundness, as though the muscular structure of the organ were insufficient to give it a characteristic shape, and perhaps also because the equal muscularity of the two sides tends to prevent the development of any asymmetry.

Since it has been possible to obtain electrocardiographic tracings from abortions and from premature infants, and even to take records from leads placed about the mother's body, data are available as to the electrical impulses of the fetal heart long before birth. Tracings from such sources have occasionally been registered as early as the end of the fourth month of gestation,^{57,58} and are always obtainable in late pregnancy if sought for with sufficient care. They give, however, little more testimony than the rate and rhythm of the fetal pulse, and often cannot be analyzed for the various components of the usual adult tracing. Sometimes, even under such circumstances, surprisingly complete curves can be secured. More delicate registration has been obtained experimentally from electrodes attached directly to the embryo, as can be done with the chick in the incubating hen's egg.^{59,60} Such material has been studied with sufficient accuracy so that it is possible to state that "by the fourth day of incubation the embryonic electrocardiogram was practically identical with that of the adult hen."¹ Observations of this nature cannot, of course, be made with human material, but what tracings have been taken from aborted embryos and fetuses directly after delivery indicate that during embryonic life the human organism seems to develop all the waves visible in the adult electrocardiogram. Nevertheless there are wide variations

observable, particularly in the tracings of premature infants, so that Rähkä,⁶¹ after examining 45 such records came to the conclusion that nothing which could be called a "typical premature electrocardiogram" exists.

The most characteristic single feature of neonatal electrocardiograms (and this is equally notable in those from premature infants) is the evidence of right ventricular preponderance.⁶²⁻⁶⁵ Although the anatomical measurements given in tabular form above indicate that the left heart has physically outgrown the right by the age of a month (or even of two weeks) this dominance of the right ventricle in the electrocardiogram does not yield to the development of left ventricular preponderance until the infant is between two and three months of age. The actual pattern of the complexes until that time is marked by a very deep S wave in Lead 1, and a low R wave in the same lead. Most workers have encountered peculiarities in the T wave, Krumbhaar and Jenks⁶² even stating that in the records of none of five infants examined by them during the first week of life was a T wave even present. In one tracing obtained by them at birth this wave did appear but only to disappear with the cutting of the cord. After the first three weeks of life, proper T waves were observed by these authors in the tracings of all infants. Other observers have made note that in the newborn this feature is frequently but by no means consistently missing; thus it was absent or only present as a trace in about 20 per cent of the infants studied by Hori, Imai, and Sato,⁶⁵ and it was lacking in 60 per cent of Seham's⁶⁴ series of newborn infants.

The significance of T wave changes is not very clear. Although their absence suggests myocardial disturbance or damage, it must be admitted that this relationship is not necessarily true, and that the T wave is more susceptible to unexplained changes than is any other part of the ventricular complex. Alteration of this part of the electrocardiogram may be considered as another evidence of the adjustment phase through which the neonatal organism is passing. Wiggers, who has published a useful review of the subject¹⁰ in the White House Conference volume dwells upon the frequency with which extra-systoles are observed in tracings made in the first days of life. Such irregularities are probably to be considered normal manifestations of the neonatal heart since they can be found in perhaps a third of tracings.

Consideration must also be given to the frequency with which adventitious sounds are heard over the heart in the first days of life. The rapid clock-like neonatal heart sounds may often be accompanied by murmurs, as is shown by the statistics of Lyon and

his colleagues,⁶⁶ who heard a murmur over the heart in about 2 per cent of 7700 infants examined during the first week. The statistical significance of this frequency probably depends upon what one calls a murmur, for another author,⁶⁷ who examined the hearts of a smaller number of newborn infants, states that 25 per cent of them had murmurs, and in another series a frequency of 34 per cent is reported.⁶⁸ Such murmurs practically always disappear within a few days or weeks after birth.

In general, these non-pathological heart murmurs tend to be systolic in time and to be heard most loudly over the apex, although occasionally the base of the heart is the region of loudest involvement. The abnormality may not always present itself at birth and disappear thereafter, for one frequently finds normal sounds for the first several days yielding to a brief interlude of abnormality which in turn passes away. Although murmurs during the neonatal period may be considered evidences of physiological readjustment in and near the heart, it must be remembered that such sounds are also frequently heard over the hearts of older children where, although they do not signify disease, they cannot be ascribed to any alteration in the routes of blood currents through the heart. In the neonatal period (as in later childhood) the mistake is often made of attaching pathological significance to these abnormalities. Accompanying evidences of circulatory disturbance should be sought before heart murmurs are evaluated in the first days of life. On the other hand, more disturbing situations have been known to arise in which the cardiac cycle is so normal upon auscultation at birth that the infant is certified as without defect, whereupon there appears a few days later a lasting murmur caused by cardiac malformation. Thus, neither the presence nor the absence of a heart murmur on any particular day of newborn life may be considered, by itself, as evidence of absolute clinical significance.

There exist certain definite, although poorly measured, differences between the vascular system in infancy and in adult life, and most of these are especially noteworthy at the neonatal stage of development. After the functional adjustment from the fetal to the extra-uterine circulation has been made, there remain peculiarities in the distribution of the blood. It has been stated, and with reason, that the premature infant probably suffers from a "*plethora visceralis*"⁶⁹ or pooling of blood in the abdominal organs, especially the liver and the spleen, which are frequently palpable in the normal infant at this time. The consequence is a poor distribution of blood to the periphery. Eckstein⁶⁹ has published a roentgenogram of a $5\frac{1}{4}$ pound (2400 grams) stillborn infant made after injection



FIGURE 15

Injection preparation showing the arterial system and the relative sizes of its vessels, in a $5\frac{1}{4}$ lb. stillborn infant. (Eckstein, *Ztschr. f. Kinderh.*, 54: 317, 1933.)

preparation to visualize the arteries. The vascular shadows to the extremities are very delicate in contrast to those in the abdomen, and the peripheral vessels are small by contrast with the peripheral vessels visualized in the body of the adult studied in the same manner. Preparations of this sort are also instructive as they indicate how much larger and more numerous are the pulmonary arterial vessels in the adult than in the newborn.

Of perhaps more importance in appraising the biology of the tissues themselves is information about the capillaries and their function. In this respect the full-term infant has been the object of less study than has the premature, but some findings throw light upon both groups. In infants of nine months' gestation a demonstrably larger number of capillaries per unit of tissue has been found in the liver and in the brain, as compared with a poor capillary vascularity of the same tissues at earlier premature birth; while at ten fetal months the capillary development is again proportionately ahead of that found at nine.^{70,71} This is known from morphologic study of dead tissues, although in the living infant developmental differences between the premature and full-term subject have not always been so sharply evident. Indeed, the capillaries of fifty premature infants when studied directly in the living skin (nail bed) showed, according to Sanna,⁷² no characteristic differences from the appearance of comparable vessels in full-term infants, nor were the capillaries of premature infants unusual in regard to their resistance against changes in pressure. However, the terminal vessels of both premature and full-term babies were observed to be somewhat limited as regards the regular distribution of finer loops, only the broader arches being demonstrable during the first few weeks after birth, with a gradual differentiation later into finer structures.

Yllpö⁷³ has made studies the results of which seem much more in keeping with clinical observation. He states that during the application of suction over the skin, hemorrhages indicating a lack of capillary resistance appeared in response to a vacuum of only -150 mm. Hg in premature infants weighing less than 1 Kg. For infants of 2 to 2.5 Kg., -400 mm. was required to produce this effect, and those weighing more than 3 Kg. did not show capillary hemorrhages until subjected to negative pressures of -500 or more mm. of mercury. This is evidence of a great deal of significance if it can be applied to the pressures exerted by the laboring uterus upon the infant's skull and body during birth. Bernfeld⁷⁴ has entirely substantiated Yllpö's finding that as the fetus grows larger and more mature *in utero* its capillaries become more resistant to pressure. It is interesting that after birth the development

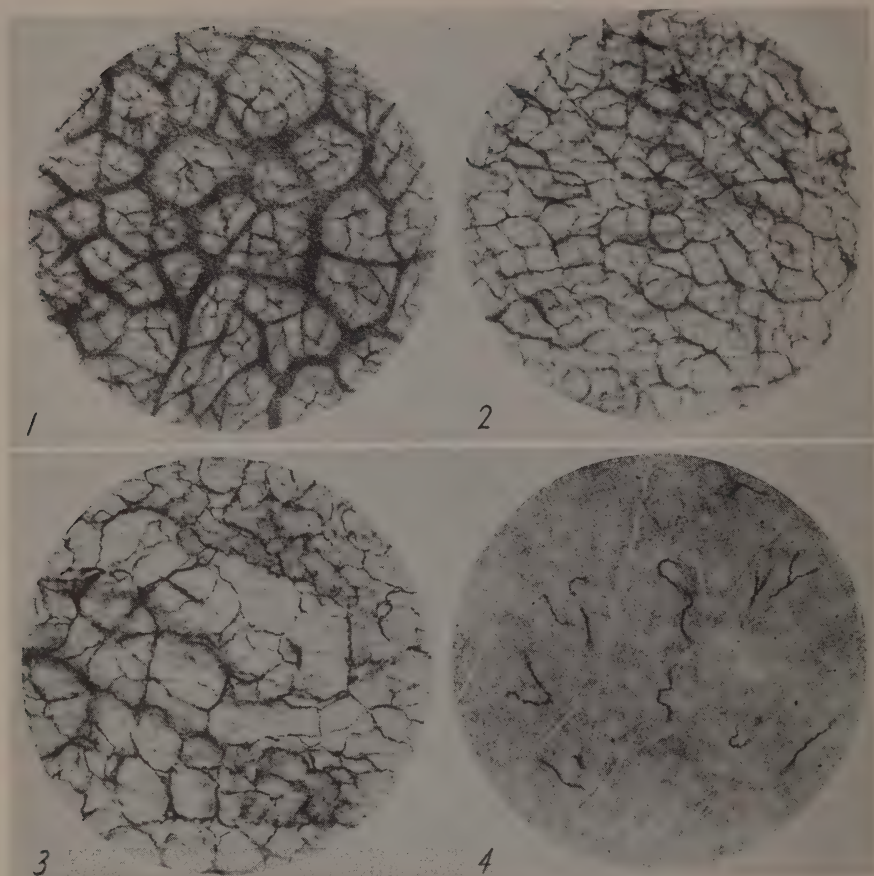


FIGURE 16

Capillaries of the neonatal skin. Schwalm, from whose work the figures are reproduced, classified the four stages as follows:

Stage 1. Apparently the earliest degree of development. Numerous broad blood vessels form a dense network with abundant anastomoses against livid red background. Between these vessels of the subpapillary plexus, capillaries are already visible but as yet without tortuosities or curves. Their caliber is fairly uniform and easily distinguishable from the caliber of the deeper vessels.

Stage 2. The background is now more reddish yellow and lighter than in 1. There the plexus vessels predominated while now the capillaries themselves form a closely woven net of very delicate vessels which are already tortuous. Their caliber is fairly uniform. In the deeper layers, subpapillary vessels are still occasionally visible.

In *Stage 3* such vessels are no longer recognizable. At best their presence can be assumed from variations in the color of the background which elsewhere has assumed a more yellow hue. The number of visible capillaries is now reduced as compared to 2. They are more tortuous, no longer so uniform in caliber, and arranged in a wider mesh.

seems to be reversed. The skin of a normal infant of a few days may withstand negative pressure as great as -600 mm. Hg without signs of capillary damage, but by two years later the critical level will have fallen to one of -250 to -400 mm.⁷⁵ If one may speak teleologically, it is as though the fetus were supplied with an increasing resistance in preparation for meeting the stresses of birth, and as though the infant were allowed to cast off this protection thereafter. At any rate, capillary hemorrhages observable in the skin of a mature baby after birth must be taken to indicate either a serious departure from the normal integrity of vessel walls, an unusually difficult delivery, or an abnormality of the blood itself by which it is able to ooze through a capillary wall capable of retaining ordinary blood.

That the capillaries of the premature tend to differ in their functional responses from those of the infant born at term has been stated by Eckstein,⁶⁹ who observed that, although the capillary contraction following a cold stimulus was prompt in a group of prematures studied, the reflex dilatation which should follow warming was delayed, often for a latent period of 60 seconds or more. Eckstein did not observe capillary changes accompanying cyanosis of the skin in the premature, so that he doubted whether peripheral circulatory alterations had anything to do with cyanosis in such infants.

Excellent representations of the size and form of the cutaneous vessels have been printed by Schwalm,⁷⁶ who showed that the appearance of the skin of the chest, seen through a capillary microscope, can be classified in four fairly definite developmental groups or stages. He studied 83 infants, most of them after full term gestation. Many were repeatedly observed on several occasions. His tabulation indicated the preponderance of the so-called developmental Stages 1 and 2 during the first two days of life, whereas the pattern listed as Stage 3 was first observed somewhere between the second and the eleventh days; and in one instance not until the seventh week. The more or less adult vessel distribution of Stage 4 was not observed in the skin of any infant younger than five weeks. This author described very circumstantially the manifestations of the

In some infants past the neonatal period, a capillary picture as shown in *Stage 4* was observed. The background is light yellow without any red overtone, traversed by straight refractile clefts in the horny layer of the skin. The field contains only single capillary loops which run a tortuous course and disappear again in the background. This appearance forms a transition to the capillary pictures of the skin of the chest in adults. (Schwalm, *Arch. f. Kinderh.*, 103: 129, 1934.)

skin vessels during cyanosis as it occurs with crying. In these full-term infants, at the beginning of macroscopically visible cyanosis the background was observed through the microscope to grow darker, the capillaries to become increasingly filled with blood, and, in contrast to what is said of premature infants, the visible capillaries to increase in number.

The only discoverable report of capillary blood pressures in the newborn was published by Rominger.⁷⁷ He observed, by indirect methods, pressures of 7 to 9 mm. Hg, which persisted in spite of transient functional or experimental alterations in arterial pressure, and changed but little with bodily growth. The very low magnitude of these figures, compared with direct measurements made upon the capillaries of human adults⁷⁸ casts considerable doubt on their validity. The work of Landis indicates that capillary pressures in the skin of adults are about three times those quoted for the newborn. Indeed, since the osmotic pressure exerted by the blood proteins at birth must be at least 20–25 mm. Hg, capillary blood pressures of 7 to 9 mm. would probably be insufficient to prevent osmotic forces from drawing all tissue fluids into the blood vessels.

Under the limitations of present knowledge, nothing can be said of neonatal capillary permeability for electrolytes and fluids. That this may be increased, in parallel with capillary fragility and tendency to hemorrhage, in premature infants, would seem probable.

THE DYNAMICS OF CIRCULATION

"The pulse rate," says Barcroft⁵ "is of much the same order in the fetuses of most animals so far investigated and has no relation to the ultimate pulse rate in the adult. This may be faster than the fetal pulse rate, as in the case of the rat and birds, or much slower, as in the case of man and the ox." There may be some indication in this that a more or less uncontrolled and fundamental speed

TABLE 12
PULSE RATE⁵

Species	Fetus	Newborn Period	Adult
Man	135–150	121	70
Ox	161	141	50
Dog	120–170	160	100
Goat	120–246	145–240	
Rat	96–256		184–264
Monkey	100–200		140–240

governs the circulation until birth, after which there comes about by gradual development some sort of individual control required to meet the needs of the various species.

For general observations on the human fetus and infant, the pulse rates based upon those listed by Vierordt⁷⁹ may be assumed to be accurate.

TABLE 13

Age	Pulse Rate
Fetal	130-160
Birth	180
10 min. after	170
15 min. to 1 hr.	134-136
1 day	123-126
1-8 days	124-125
1 week	124-130
2 weeks	133
2 months	130-133
6-12 months	113-127

Despite popular supposition, the human heart beats no faster in female than in male fetuses.⁸⁰ The rate tends to decline from the fourth to the eighth lunar month and then to accelerate slightly until birth. Feldman⁸¹ and Balard,⁸² have especially noted a drop in pulse rate of some 50 beats per minute from the time of birth to a low point an hour or more thereafter. Feldman mentions as though of ordinary occurrence, instances in which the pulse falls to 95 or even to 70 per minute immediately after delivery, but such changes have not frequently been encountered by others. Whatever retardation of pulse does occur after birth tends to parallel the concomitant decline in body temperature; as the pulse rises on the second day of life, the temperature rises too. A series of figures collected by Benedict and Talbot⁸³ incidental to their study of metabolism in the newborn is in general agreement with this observation. These figures, which are here condensed from the authors' Table 19, were obtained at the periods of minimum heat production during the first days of life in more than 100 infants. While no data were given for the fetal hearts at birth, that rate can be assumed to have been between 120 and 140. The figures do not necessarily present the minimum rate of the infant; they give the rate observed daily when the heat production was least, and thus while body conditions approached a basal state. They show a fall of about 20 heart-beats a minute from the fetal level to that at some degree

TABLE 14
PULSE RATES OF INFANTS DURING MINIMAL METABOLISM

Day of life	1	2	3	4	5	6
Maximum Pulse Rate in any Infant	129	138	144	132	134	138
Minimum Pulse Rate in any Infant	96	88	82	98	96	106
Average Pulse Rate	112	114	116	116	116	122

of metabolic rest during the first extra-uterine day. Since fetal metabolism calls for little heat production, the lower pulse rate occurring with transfer from that condition to an extra-uterine one of even minor heat production suggests some other explanation for a falling pulse than that of metabolism, and probably the altered mechanical aspects of circulation produce the change.

The infant's pulse is notoriously irregular, and capable under exertion of great rapidity so that rates of 180 and more beats per minute are frequently observed during periods of noisy activity. Benedict and Talbot⁸⁴ have presented charts, one of which is reproduced here, showing the extreme variation of the pulse rate for 12 hours of early life. Wiggers¹⁰ has stated that "during no period of life is the heart beat so truly an intrinsic affair as during infancy. No evidence exists that the intrinsic nerves exert any tonic influence. The rate is therefore rapid, and is subject to further increase only through thermal and chemical stimuli carried by the blood stream. The vagus mechanism is functional, however, and when stimulated through infections or an increase in intracranial tension may cause a slowing of the heart." More investigation of

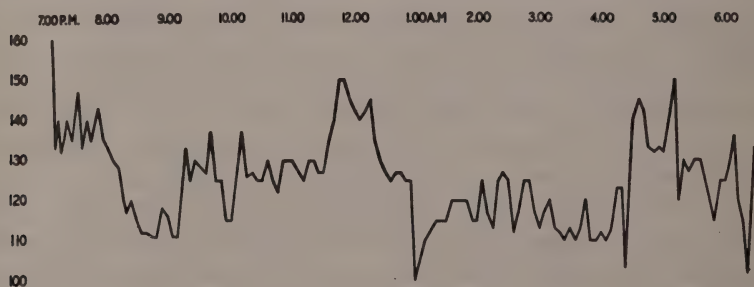


FIGURE 17

Instability of the neonatal pulse rate. Observations made from 7 P.M. to 7 A.M. upon a normal infant of 3 days, weighing $9\frac{1}{2}$ lb. Highest rates usually, thought not always, associated with some bodily movement. (Benedict and Talbot: *The Gaseous Metabolism of Infants*, Washington, Carnegie Institution. Publication Number 201.)

the nervous control of cardiac rate in early infancy would be of interest and value.

If the volume of blood pumped by the heart of the newborn infant conforms to the principles of adult circulation, it should equal (in liters per minute) the body surface in square meters multiplied by the constant factor 2.2.⁸⁵ Thus computed, one ventricle of the heart of a 3.5 Kg. infant should pump about 520 cc. per minute or between 4 and 5 cc. per beat. No actual data are available by which this figure can be substantiated. Wiggers¹⁰ offers a cardiac output estimate of between 240 and 350 cc. while Feldman,⁸¹ after a long calculation arrives at an amount of 1000 cc. per minute. This is, however, based on at least one assumption and one definite error. If this error be corrected (by substituting 20 instead of 49 cc. for tidal air) the calculation works out to about 500 cc. volume flow per minute, which agrees well enough with the estimation of 520 cc. arrived at from surface area.

On the basis of the increased oxygen consumption of infants as compared with adults, Brock⁸⁶ has computed the minute volume of blood from the infant's heart to be slightly more than twice that of the adult, when expressed in cc. per kilogram of body weight. Taking a figure of 62 cc. per kilo as the average for the adult⁸⁷ the calculation works out:

$$62 \times 3.5 = 217 \text{ cc.}$$

$$217 \times 2 = 434 \text{ cc.} = \text{Volume flow per minute in newborn.}$$

Seckel,⁸⁸ using the histamine technique of Weiss, obtained a probable circulation time of 28 to 34 seconds in the first two years of life; on the basis of this and a blood volume figure which may have been slightly high, he arrived at an average cardiac output per minute in infancy at 165 cc. per kilo or about 520 cc. in the case of an average newborn baby. In the present state of our knowledge it can be hazarded that in the neonatal period the cardiac output per minute is somewhere between 440 and 520 cc. of blood. The one thing certain is that here again the infant pays for his small size by meeting the demands of proportionately large surface area.

Is this cardiac output greater or smaller than that which the fetal heart was delivering before birth? The answer cannot be given; even had fetal measurements been made, their comparison with post-natal values would be difficult. For, as Barcroft⁵ has had the ingenuity to note, the cardiac output is usually stated as that of one ventricle per minute, while in fetal life the *ductus arteriosus* causes both ventricles to pour their blood (in unmeasured proportions) into the aorta at once.

The circulation time of the newborn human infant needs investigation. Feldman⁸¹ cites Vierordt's demonstration that "no matter what the pulse frequency in any class of animals may be, the circulation time equals twenty-seven heart beats." With a pulse rate of 134 on the first day of life the calculation $\frac{27}{134} \times 60$ equals 12 seconds. If the more basal pulse rate of 112 (Table 14) be substituted for 134, the circulation time becomes about 14.5 seconds on the first day as compared with an adult figure, arrived at by the same method, of 22 seconds. Haselhorst and Stromberger⁸⁹ tried to secure data immediately after birth, while the fetal state must still in part have obtained. They introduced Congo red dye into the umbilical vein of the pulsating cord and measured the time elapsing before the dye reappeared at the same site. The observers found that in one series of infants born in the normal manner this period was 60 seconds, while in others delivered by elective Caesarean section from the non-contracting uterus, the time was 30 seconds. It is probable that the actual value lies somewhere between. The circulation so measured must have included the extensive circuit of the placenta as well as that through the body; on the other hand, in the body the dye need not have gone completely around the systemic and pulmonary circuits. Even a small amount of mixing of crossed streams in the heart or a minor flow through the *ductus arteriosus* would have resulted in the shunting of dye directly back to the cord vessels, so that these measurements, while representing the speed with which some blood flows into and out of the fetal body and around the placenta, probably do not indicate that of blood taking other and longer courses.

Hubbard and others,⁹⁰ in a few infants, measured the speed with which radioactive material injected into the veins of one arm made its presence in the contra-lateral hand known by registering on a Geiger counter. The material must have passed to the right heart, gone around the pulmonary circuit, and returned to the body from the left heart, although it probably registered its presence while it was still in the artery supplying the hand. Thus the time measured could not include the complete round of the systemic as well as the pulmonary circuit. The time for the youngest patients (six weeks of age) was between three and twelve seconds, with an average of seven seconds. The subjects were not newly born. There is so much difference between these figures and those for the infant (and placenta) at birth, that data obtained by some method such as the use of radioactive material in infants on the first or second day would be most welcome. The difficulties of using any method are obviously great.

FETAL AND NEONATAL BLOOD PRESSURES

Several observations indicate that the fetal blood pressure follows a steady increase during the later months of gestation. Thus, Woodbury, Robinow, and Hamilton⁹¹ have recorded the pressure within the umbilical artery at the time of premature birth to be as follows:

Fetal Age	5 mos.	5 mos.	6½ mos.	7 mos.	8 mos.	9 mos.
Systolic/Diastolic	33/	39/21	55/25	70/35	85/45	80/46

The regularity of the rise is interesting and may be compared with that observed by Barcroft and Kennedy⁹² in the fetal sheep, in which subjects the systolic pressure in the arteries rises more sharply as term approaches than was the case in these few human observations. The human fetal blood pressure rises steeply between the fifth and seventh month, then slowly until the ninth; since the gestation period of the sheep is shorter by some months than that of the human infant, the more gradual blood pressure rise in late human fetal life may represent a phase of fetal life not to be found in the animal. In neither species is the rate of rise in blood pressure maintained after birth.

The effects upon the fetal blood pressure of certain processes associated with birth are of some interest, particularly the result of cord ligation, of extra-uterine respiration, and of the forcible intrathoracic changes of crying. The fetal sheep responds to clamping of the cord with an immediate elevation of its blood pressure.⁶ Again, such a fetus may differ from the newborn human infant; it may possess an intact utero-placental connection providing it with a suitable amount of oxygen until the moment of interference with the cord. Or the fetal sheep may have developed vaso-pressor mechanisms which are not present in certain other species (including the human) at birth. In any event, clamping of the human umbilical cord was not followed by important pressure changes in the umbilical arteries of newborn infants studied by Haselhorst.³⁶ Nor was there any difference in three infants of another series⁹¹ unless the cord was clamped very near the recording cannula, which in one instance increased the pressure only from 88 to 91 mm. Hg.

It seems quite well proven that occlusion of the cord at the delivery of the human infant does not alter the blood pressure within it or elsewhere in the body. As to the response to the onset of respiration there is lack of agreement. Barcroft⁶ has not only recorded a rise in the femoral arterial pressure of the sheep at the onset of

respiration after delivery but has explained how this might be brought about by cardio-accelerator and vaso-constrictor mechanisms when stimulated by afferent impulses from the lungs. Consistent changes in pressure in the umbilical arteries of human infants at respiratory onset have not been observed, although Haselhorst³⁶ recorded some elevations in the pressure, but these occurred only if respiration was accompanied by crying. This was also noted in the investigations of Woodbury⁹¹ who measured the effect upon the umbilical arterial pressure produced by crying. The systolic and diastolic pressures were increased equally and by an average of 27 mm. Hg. The fact that in a newborn organism such an increase could be superimposed upon a systolic level already as high as 80 mm. is a little surprising, although in keeping with what is known of the intra-thoracic pressures attainable even by premature infants.

Before comparing the general levels of pressure during and after birth, something may be said of the pressure relationships in the right and left sides of the fetal and neonatal heart. Wiggers⁹³ states that in adults the pulmonary or right ventricular systolic pressure is about one-third of the systemic or left ventricular. There is abundant proof from dynamic and anatomic studies that equality is maintained between the pressures of both sides of the fetal heart. Pohlmann¹¹ ascertained that fluids rose to equal heights in tubes inserted into the two ventricles of fetal animals, while the ventricular size and musculature have been shown to be as great on the right as on the left. According to Patten⁷ the right ventricular musculature is even greater in the heart of a human fetus than is the left, as may well be the case since blood has to be pumped from the right ventricle to the aorta through the ductus. Photographic sphygmomanometer records¹² have shown simultaneous pressures of 21 and 20 mm. respectively in the right and left ventricles of fetal rabbits. It is not known how soon after birth the pulmonic pressure of the human heart falls behind the rising systemic so as to bring about the difference mentioned at the beginning of this paragraph. Animal experiments do not indicate the rather sudden adjustment occurring more or less immediately at birth, which was formerly thought to take place, but point to a slower process. The data below have been obtained upon rabbits.¹²

Haselhorst³⁶ found the pressure in the umbilical artery before the human infant was removed from the uterus at term to be 68 mm. Hg, and in several instances immediately after delivery to be 75 mm. (extremes 46 and 110 mm.) in the same vessel. American

workers⁹¹ have recently found the average pressures in the umbilical arteries of 24 normal babies immediately after birth to be 80.1/46.3 mm. Hg, a systolic reading in reasonable agreement with that of Haselhorst, the slight difference being perhaps due to the treatment of the cord. It appears to have been clamped, although well below the point of the recording cannula, in those investigations yielding the higher figures, while in the other series the circulation was not thus arrested. There is evidence that the pressure in the umbilical artery accurately represents that of intra-ventricular systole in the

TABLE 15
VENTRICULAR PRESSURES IN MM. HG (NEWBORN ANIMALS)

	Before Respira- tion	After Respiration		Age 2 Days		Adult
		Insp.	Exp.	Insp.	Exp.	
Right Ventricle S/D	21/0	16/1	24/3	18/0	20/4	25/
Left Ventricle S/D	20/1	28/0	30/3	27/2	47/11	140/

heart. Simultaneously recorded findings from one cannula in the umbilical artery and another in the left ventricle of a non-viable human fetus at five months have been compared and found to be in each case 39 mm. Hg at systole.⁹¹ Does the umbilical artery pressure also agree with the blood pressure in an extremity as ordinarily determined? Woodbury, Robinow, and Hamilton⁹¹ have convinced themselves that it does so, since they found directly measured umbilical artery pressures to be the same as those simultaneously obtained by cuff and palpation at the wrist. When a cuff 2.5 cm. in width was used, the systolic pressure indicated by palpation below it was exactly that recorded from a cannula in the umbilical artery. Moreover, evidence obtained by the shape of curves recorded photographically leads also to the conclusion that blood pressure measurements taken from a newborn infant's extremity with a cuff 2.5 cm. in width are accurate and representative.

The lower pressures published by many authors⁹⁴⁻⁹⁷ as normal for the newborn very probably represent errors due to improper cuffs. Salmi,⁹⁴ with a 4 cm. cuff, reported a series of blood pressures in the neonatal period which are lower than those published by Woodbury, Robinow, and Hamilton;⁹¹ while the figures published by Bowman⁹⁵ and secured with a 5 cm. cuff are still lower than those of Salmi. On the other hand, Dexter and Weiss,⁹⁸ using the

2.5 cm. cuff, found levels closely comparable with those of Hamilton and his colleagues. To show the importance of cuff size for accurate work with these patients, figures from the studies mentioned are grouped in Table 16; many other investigations have been made but the trend of all is the same.

All studies, whatever the general level of their results, show a very consistent rise in systolic pressures as neonatal age advances. The more accurate the technique, the less steep is this rise. In general the systolic pressure is increased by about 10 mm. during the first twenty-four hours of life, and by another 10 mm. between the first and tenth days, the properly obtained level at the end of that time being roughly 95 to 100 mm. This trend is obviously not maintained at any such rate after the newborn period, in fact the only available series of figures by a single observer in which apparatus of the same type has been used to follow the pressures of children from birth through adolescence shows that while the systolic pressure rises nearly 20 mm. from the first to the 14th day, there is a further change of only 2.5 to 5 mm. during all the rest of the first year.⁹⁹

This arouses curiosity as to the pressures of small and of premature infants. Several authors^{96,100} have stated that in general a direct relationship exists between the weight and the blood pressure of the child at birth. As shown at the bottom of the foregoing table, Bowman⁹⁵ found prematures weighing less than three pounds to have average pressures of 45/39 mm. Hg, those of three to four pounds 46/31, whereas a group of six to seven pound infants had an average blood pressure of 62/41. All of these values were obtained on the fourth day of life, and all must be lower than the actual pressures because the author used a wide cuff. Indeed, the matter of cuff size throws doubt on most of the figures for premature infants, since even a 2.5 mm. cuff would be so wide that its use could result in a falsely low figure for a baby of only three pounds. Salmi denies the existence of any constant relationship between blood pressure and birth weight, although he admits that a parallelism occasionally occurs. He cites an infant weighing less than 2 Kg. (4.4 lb.) whose blood pressure on the first day was equal to the average for the general group of full-term subjects.

Less can be said of the diastolic than the systolic pressure, but diastolic pressures seem to lie between about 30 and 46 mm. Hg at birth. While the systolic pressure is making its 20 mm. increase during the next two weeks the diastolic may gain a little less in elevation, so that the pulse pressure of about 35 mm. at birth may increase very slightly in the succeeding period.

CLINICAL SUMMARY

Although the clinician will rarely be faced with situations demanding knowledge of the circulation of blood before birth, it may nevertheless be worthwhile to summarize that subject here. Apparently, the crossing of blood streams in the human fetal heart cannot now be denied, while, on the other hand, the amount of blood flow through the lungs before birth cannot yet be estimated. The closure of the *ductus arteriosus* appears to be brought about by local response to increase in blood oxygenation at birth. However complicated are the circulatory readjustments required for post-natal life and however prolonged the interval for their complete and final accomplishment, a period of only three hours or less is required before the circulation behaves like that of an adult in terms of the distribution of oxygenated blood. In the rare child in whom the necessary adjustments fail to occur, the explanation must probably be a morphological maldevelopment, although in the case of patent *ductus* a period of post-natal anoxia might be suspected as a cause.

Post-natal bleeding from the umbilical vessels is resisted by local muscular contracture resulting from elevation of blood oxygen, mechanical stimuli, and cooling. Were the human infant left with a long remnant of umbilical cord at delivery, it is probable that clamping and tying would be needed no more than at the birth of other animals.

The blood volume at birth appears to be similar to that of the adult, or about 10% of body weight, and is subject to alterations of one-fourth to one-third of its total amount depending upon whether the infant recovers the 100 to 125 cc. of its blood which is momentarily in the umbilical and placental vessels. The infant is able to adjust to the effects of early or delayed clamping of the cord with very little evidence of advantage or disadvantage. Somewhat less labor is required of the heart after birth than before, in that the abandonment of placenta and cord allows a smaller quantity of blood to be propelled a shorter distance. On the other hand, increased muscle tone probably calls for an extension of cardiac work, whereas the demands of comparatively great body surface require a neonatal cardiac output of about 500 cc. per minute. This is greater in proportion to body weight than the output of the adult heart.

The heart is thus relatively large at birth but grows less rapidly thereafter, so that the cardio-thoracic index as a roentgenological measure of normal heart size cannot be applied to young infants. A better standard than 50% of thoracic diameter as an upper limit

of normal cardiac diameter is an absolute maximum figure of 5.5 cm. On the other hand, roentgenological or other evidence of progressive enlargement after birth is of serious significance. As further effects of fetal life and post-natal readjustment, the electrocardiogram normally shows right ventricular preponderance in the first two or three post-fetal months, and frequently presents extra-systoles and variable or absent T waves. Cardiac murmurs may occur in as many as one-third of all newborn infants, but the great majority are transitory and do not signify permanent abnormalities. Conversely, significant murmurs may not become established immediately after birth.

Although the average pulse rate during the neonatal period falls from the more rapid one of fetal life to about 125 to 130 per minute, variability is so marked that rates of 90 or of 180 may occur for brief periods in quite normal babies. The blood pressure of 80/46 in the umbilical arteries rises by about 10 mm. during the first 24 hours and the systolic pressure usually reaches 95 to 100 mm. Hg at the 14th day. Accurate readings require a cuff of 2.5 mc. (1 inch) diameter, while an even narrower one ought to be used for premature infants, whose systolic blood pressures are normally 60-80 mm. Hg.

By comparison with older subjects, the vascular distribution in the newborn seems to favor a central pooling of blood and a paucity of circulation to the periphery, the internal trunks and the arteries to the abdominal viscera being relatively larger than those to the extremities. Capillary networks, as seen in the skin, appear to be coarse and to lack the finer control mechanisms they acquire later. The number of capillaries is smaller and the resistance of their walls weaker after premature than after full-term birth. Acceptable figures for capillary blood pressures and for capillary permeability to electrolytes, water, and other substances, are not yet available.

BIBLIOGRAPHY

1. WINDLE, W. F.: Physiology of the Fetus: Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders, 1940.
2. POHLMAN, A. G.: The fetal circulation through the heart... Bull. Johns Hopkins Hosp. 18: 409, 1907.
3. KELLOGG, H. B.: Studies on the fetal circulation of mammals, Am. J. Physiol. 91: 637, 1930.
4. HUGGETT, A. S.: Foetal blood-gas tensions and gas transfusion through the placenta of the goat, J. Physiol. 62: 373, 1927.
5. BARCROFT, J.: Fetal circulation and respiration, Physiol. Rev. 16: 103, 1936.
6. BARCROFT, J.: The Brain and Its Environment, New Haven, Yale University Press, 1938.

7. PATTEN, B. M.: The Circulatory System; Embryological, in Growth and Development of the Child; Part 2: Anatomy and Physiology. The White House Conference. New York, The Century Company, 1933.
8. PATTEN, B. M., and TOULMIN, K.: Certain measurements of the foetal heart and their significance, *Anat. Rec.* 45: 237, 1930.
9. ABEL, S., and WINDLE, W. F.: Relation of volume of pulmonary circulation to respiration at birth, *Anat. Rec.* 75: 451, 1939.
10. WIGGERS, C. J.: The Circulatory System; Physiological, in Growth and Development of the Child; Part 2: Anatomy and Physiology. The White House Conference. New York, The Century Company, 1933.
11. POHLMAN, A. G. The course of the blood through the heart of the fetal mammal, with a note on the reptilian and amphibian circulations, *Anat. Rec.* 3: 75, 1909.
12. HAMILTON, W. F., WOODBURY, R. A., and WOODS, E. B.: The relation between systemic and pulmonary blood pressures in the fetus, *Am. J. Physiol.* 119: 206, 1937.
13. BARCLAY, A. E., BARCROFT, J., BARRON, D. H., and FRANKLIN, K. J.: Radiographic demonstration of circulation through heart in adult and in foetus, and identification of ductus arteriosus, *Brit. J. Radiol.* 12: 505, 1939.
14. BARCLAY, A. E., BARCROFT, J., BARRON, D. H., FRANKLIN, K. J., and PRICHARD, M. M. L.: Studies of foetal circulation and of certain changes that take place after birth, *Am. J. Anat.*, 69: 383, 1941.
15. WHITEHEAD, W. H.: A working model of the crossing caval blood streams in the fetal right atrium, *Anat. Rec.* 82: 277, 1942.
16. WINDLE, W. F.: Physiology and anatomy of the respiratory system in the fetus and newborn infant, *J. Pediat.* 19: 437, 1941.
17. SCAMMON, R. E., and NORRIS, E. H.: On the time of the post-natal obliteration of the fetal blood passages (foramen ovale, ductus arteriosus, ductus venosus), *Anat. Rec.* 15: 165, 1918.
18. CHRISTIE, A.: Normal closing time of the foramen ovale and the ductus arteriosus, *Am. J. Dis. Child.* 40: 323, 1930.
19. KIRSTEIN, F.: Der Verschluss des Ductus Arteriosus, *Arch. f. Gynäk.* 90: 303, 1910.
20. GRÄPER, L.: Die anatomischen Veränderungen kurz nach der Geburt, *Ztschr. f. d. ges. Anat.* 61: 241, 1921.
21. LINZENMEIER, G.: Der Verschluss des Ductus Arteriosus Botalli nach der Geburt des Kindes, *Ztschr. f. Geburtsh. u. Gynäk.* 76: 217, 1914.
22. STRASSMANN, P.: Anatomische und physiologische Untersuchungen über den Blutkreislauf beim Neugeborenen, *Arch. f. Gynäk.* 45: 393, 1894.
23. ROEDER, H.: Die Histogenese des arteriellen Ganges, *Arch. f. Kinderh.* 33: 147, 1902.
24. FROMBERG, C.: Experimentelle Studie über die Zirkulationsverhältnisse im Ductus arteriosus postpartum, *Zentralbl. f. Herz- u. Gefässkr.* 7: 69, 1915.
25. VON HAYEK, H.: Der funktionelle Bau der Nabelarterien und des Ductus Botalli, *Ztschr. f. Anat. u. Entwicklungsgsch.* 105: 15, 1935.
26. VARIOT, CAILLIAU, and BREZEZICKI: Recherches sur le mode d'Oblitération du canal artériel, *Arch. de. méd. d. enf.* 24: 537, 1921.

27. MÉLKA, J.: Beitrag zur Kenntnis der Morphologie und Obliteration des Ductus arteriosus Botalli, *Anat. Anz.* 61: 348, 1926.
28. SWENSSON, A.: Beitrag zur Kenntnis von dem histologischen Bau und dem postembryonalen Verschluss des Ductus arteriosus Botalli, *Ztschr. f. Mikr. Anat. Forsch.* 46: 275, 1939.
29. KENNEDY, J. A., and CLARK, S. L.: Observations on ductus arteriosus of guinea pig in relation to its method of closure, *Anat. Rec.* 79: 349, 1941.
30. KENNEDY, J. A., and CLARK, S. L.: Observations on physiological reactions of ductus arteriosus, *Am. J. Physiol.* 136: 140, 1942.
31. SCAMMON, R. E.: Summary of the Anatomy of the Infant and Child. Chapter 3, Volume 1, *Pediatrics*, edited by I. A. Abt. Philadelphia, W. B. Saunders Company, 1923.
32. PATTEN, B. M.: The closure of the foramen ovale, *Am. J. Anat.* 48: 19, 1931.
33. RÄIHÄ, C. E.: Über einige Neugeborenenprobleme (vorläufige Mitteilung), *Acta paediat.* 28: 390, 1941.
34. NIKITIN—Cited by Feldman, W. M., *Ante-natal and Post-natal Child Physiology*. London, Longmans, Green, & Company, 1920.
35. WILLIAMS, W. L.: *Veterinary Obstetrics*, 2nd Ed., Ithaca, New York, 1931, published by the author.
36. HASELHORST, G.: Über den Blutdruck in den Nabelschnurgefäßen, die Ausschaltung des Nabelschnur- und Plazentarkreislaufs nach Geburt des Kindes und über den Blutstillungsmechanismus, *Ztschr. f. Geburtsh. u. Gynäk.* 95: 400, 1929.
37. SCHMITT, W.: Über die Bedeutung der intrauterinen Atembewegungen beim Fötus, *Ztschr. f. Geburtsh. u. Gynäk.* 90: 559, 1926-27.
38. KROGH, A.: *The Comparative Physiology of Respiratory Mechanisms*, Philadelphia, University of Pennsylvania Press, 1941.
39. RECH, W.: Untersuchungen über den physiologischen Verschluss der Nabelschnurarterien, *Ztschr. f. Biol.* 81: 487, 1925.
40. CATTANEO, L.: Sul meccanismo di chiusura fisiologica dei vasi del cordone ombelicale, *Ann. di ostet. e ginec.* 57: 319, 1935.
41. SNELLING, C. E.: Round table discussion on hemorrhage in the newborn, *J. Pediat.* 20: 637, 1942.
42. ELLIOTT, R. H., HALL, F. G., and HUGGETT, A. St. G.: Blood volume and oxygen capacity of foetal blood in the goat, *J. Physiol.* 82: 160, 1934.
43. KRAFKA, J., Jr.: Interplay of piestic factors at birth, with consideration of their physiologic and clinical significance, *Am. J. Dis. Child.* 45: 1007, 1933.
44. BUDIN, P.: A quel moment doit-on pratiquer la ligature du cordon ombilical? *Progrès. Méd.* 3: 750, 1875, and 4: 2, 1876.
45. SCHÜCKING, A.: *Zur Physiologie der Nachgeburtsperiode. Untersuchungen über den Placentarkreislauf nach der Geburt des Kindes*, *Klin. Wehnschr.* 14: 18, 1877.
46. HASELHORST, G.: Über Art und Dauer der Blutströmung in den Nabelschnurgefäßen postpartum, *Ztschr. f. Geburtsh. u. Gynäk.* 96: 487, 1929.
47. HASELHORST, G., and ALLMELING, A.: Die Gewichtszunahme von Neugeborenen infolge postnataler Transfusion, *Ztschr. f. Geburtsh. u. Gynäk.* 98: 103, 1930.

48. DEMARSH, Q. B., WINDLE, W. F., and ALT, H. L.: Blood volume of newborn infant in relation to early and late clamping of umbilical cord, *Am. J. Dis. Child.* 63: 1123, 1942.
49. LUCAS, W. P., and DEARING, B. F.: Blood volume in infants estimated by the vital dye method, *Am. J. Dis. Child.* 21: 96, 1921.
50. ROBINOW, M. and HAMILTON, W. F.: Blood volume and extracellular fluid volume of infants and children; studies with improved dye micro-method, *Am. J. Dis. Child.* 60: 827, 1940.
51. BRINES J. K., GIBSON, J. G., JR., and KUNKEL, P.: Blood volume in normal infants and children, *J. Pediat.* 18: 447, 1941.
52. GIBSON, J. G., JR., and EVANS, W. A., JR.: Clinical studies of blood volume . . . *J. Clin. Investigation* 16: 317, 1937.
53. GOODMAN, A. L.: Heart disease in infancy and childhood, *Arch. Pediat.* 33: 909, 1916.
54. FALK, A. A.: *Das Wachstum des Herzens bei Kindern*, Dissert., St. Petersburg 1901; quoted by, Gundobin, N. P.: *Die Besonderheiten des Kindesalters*, Berlin, S. Rubinstein, 1913.
55. MÜLLER, WILHELM: *Die Massenverhältnisse des menschlichen Herzens*, Hamburg u. Leipzig, L. Voss, 1883.
56. BAKWIN, H. M., and BAKWIN, R. M.: Body build in infants; growth of the cardiac silhouette and the thoraco-abdominal cavity, *Am. J. Dis. Child.* 49: 860, 1935.
57. MANN H., and BERNSTEIN, P.: Fetal electrocardiography, *Am. Heart J.* 22: 390, 1941.
58. WARD, J. W., and KENNEDY, J. A.: Recording of fetal electrocardiogram, *Am. Heart J.* 23: 64, 1942.
59. BOGUE, J. Y.: The electrocardiogram of the developing chick, *J. Exper. Biol.* 10: 286, 1933.
60. HOFF, E. C., KRANER, T. C., DuBOIS, D., and PATTEN, B. M.: Development of the electrocardiogram of the embryonic heart, *Am. Heart J.* 17: 470, 1939.
61. RÄIHÄ, C. E.: Das Elektokardiogram des Frühgeborenen, *Acta paediat.* 18: 440, 1936.
62. KRUMBHAAR, E. B., and JENKS, H. H.: Electrocardiographic studies in normal infants and children, *Heart* 6: 189, 1917.
63. HECHT, A. F.: Der Mechanismus der Herzaktion im Kindesalter, *Ergebn. d. inn. Med. u. Kinderh.*, 11: 324, 1913.
64. SEHAM, M.: The electrocardiogram in normal children, *Am. J. Dis. Child.* 21: 247, 1921.
65. (a) HORI, H., IMAI, M., and SATO, M.: On the electrocardiogram of the new-born . . . *Jap. J. Obst. & Gynec.* 18: 325, 1935.
(b) HORI, H., IMAI, M., and SATO, M.: On the electrocardiogram of the asphyxiated newborn, *Jap. J. Obst. & Gynec.* 18: 333, 1935.
66. LYON, R. A., RAUH, L. W., and STIRLING, J. W.: Heart murmurs in newborn infants, *J. Pediat.* 16: 310, 1940.
67. SIEMSEN, W. J.: Functional heart murmurs in newborn infants, *Illinois M. J.* 73: 157, 1938.
68. SEHAM, MAX.: Physical Examination of the Heart in Normal Children. Chapter 49, Volume 4, *Pediatrics*, edited by I. J. Abt. Philadelphia, W. B. Saunders Company, 1924.
69. ECKSTEIN, A.: Über den peripheren Kreislauf bei Frühgeborenen, *Ztschr. f. Kinderh.* 54: 317, 1933.

70. MALI, A. M., and RÄIHÄ, C. E.: Vergleich zwischen dem Kapillarnetz des frühgeborenen und dem des reifen Kindes . . . *Acta paediat.* 18: 118, 1935.
71. LEVINE, S. Z., and GORDON, H. H.: Physiologic handicaps of the premature infant; I. Their pathogenesis, *Am. J. Dis. Child.* 64: 274, 1942.
72. SANNA, G.: I capillari nel prematuro, *Riv. di Clin. pediat.* 32: 1430, 1934.
73. (a) YLLPÖ, A.: Pathologisch-anatomische Studien bei Frühgeborenen, *Ztschr. f. Kinderh.* 20: 212, 1919.
(b) YLLPÖ, A.: Zum Entstehungsmechanismus der Blutungen bei Frühgeburten und Neugeborenen, *Ibid.* 38: 32, 1924.
74. BERNFELD, W.: Experimentelle Untersuchungen über die Capillarresistenz junger, insbesondere frühgeborener Säuglinge (Saugglockenmethode), *Monatschr. f. Kinderh.* 51: 1, 1931.
75. ABT, A. F., FARMER, C. J., and EPSTEIN, I. M.: Normal ascorbic acid determinations in blood plasma and their relationship to capillary resistance, *J. Pediat.* 8: 1, 1936.
76. SCHWALM, H.: Die Hautkapillaren bei Neugeborenen, *Arch. f. Kinderh.* 103: 129, 1934.
77. ROMINGER, E.: Über den arteriellen Blutdruck und den Kapillardruck im Kindesalter, *Arch. f. Kinderh.* 73: 81, 1923.
78. LANDIS, E. M.: Capillary pressure and capillary permeability, *Physiol. Rev.* 14: 404, 1934.
79. VIERORDT, K.: Anatomische, physiologische und physikalische Daten und Tabellen, Jena, G. Fischer, 1906.
80. BERNSTEIN, P., and MANN, H.: Clinical evaluation of fetal electrocardiography; study of 100 cases by new technique and an improved instrument, *Am. J. Obst. & Gynec.* 43: 21, 1942.
81. FELDMAN, W. M.: *The Principles of Ante-Natal and Post-Natal Child Physiology*, Pure and Applied, London, Longmans, Green & Company, 1920.
82. BALARD, P.: La Tension Artérielle et l'oscillométrie chez le nouveau-né, *Nourisson* 9: 304, 1921, and *Compt. rend. Soc. de Biol.* 13: 483, 1912.
83. BENEDICT, F. G., and TALBOT, F. B.: *The Physiology of the Newborn Infant; Character and Amount of the Catabolism*. Washington, Carnegie Inst., 1915. Carnegie Inst., Pub. No. 233.
84. BENEDICT, F. G., and TALBOT, F. B.: *The Gaseous Metabolism of Infants, with special reference to its relation to pulse-rate and muscular activity*. Washington, Carnegie Inst., 1914. Carnegie Inst., Pub. No. 201.
85. GROLLMAN, A.: *The Cardiac Output of Man in Health and Disease*, Springfield, Illinois, Charles C Thomas, 1932.
86. BROCK, J.: *Biologische Daten für den Kinderarzt*. Erster Band, Berlin, J. Springer, 1932.
87. BEST, C. H., and TAYLOR, N. B.: *The Physiological Basis of Medical Practice*, 3rd Ed., Baltimore, William Wood & Company, 1943.
88. SECKEL, H.: Die normale Blutumlaufsdauer und Kreislaufgrösse in den ersten beiden Lebensjahren, *Jahrb. f. Kinderh.* 131: 87, 1931.
89. HASELHORST, G., and STROMBERGER, K.: Über den Gasgehalt des Nabelschnurblutes vor

- und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta, *Ztschr. f. Geburtsh. u. Gynäk.* 102: 16, 1932.
90. HUBBARD, J. P., PRESTON, W. N., and ROSS, R. A.: Velocity of blood flow in infants and young children, determined by radioactive sodium, *J. Clin. Investigation* 21: 613, 1942.
 91. WOODBURY, R. A., ROBINOW, M., and HAMILTON, W. F.: Blood pressure studies on infants, *Am. J. Physiol.* 122: 472, 1938.
 92. BARCROFT, J., and KENNEDY, J. A.: Distribution of blood between foetus and placenta in sheep, *J. Physiol.* 95: 173, 1939.
 93. WIGGERS, C. J.: *Physiology in Health and Disease*, 3rd Ed. Philadelphia, Lea & Febiger, 1939.
 94. SALMI, T.: Untersuchungen über den Blutdruck und den Reststickstoff des Blutes beim Neugeborenen, mit besonderer Berücksichtigung der Kinder von Nierengestosemüttern, *Acta paediat.* 18: 92, 1935.
 95. BOWMAN, J. E.: The blood pressure in the newborn *Am. J. Dis. Child.* 46: 949, 1933.
 96. REIS, R. A., and CHALOUPKA, A. J.: Blood pressure in the newborn following normal and pathological labor, *Surg., Gynec. & Obst.* 37: 206, 1923.
 97. RUCKER, M. P., and CONNELL, J. W.: The blood pressure in the new-born, *Am. J. Dis. Child.* 27: 6, 1924.
 98. DEXTER, L., WEISS, S., and OTHERS: *Preeclamptic and Eclamptic Toxemia of Pregnancy*, Boston, Little, Brown & Company, 1941.
 99. SLADKOF: Dissertation, St. Petersburg, 1903; cited by Feldman, W. M., *Ante-Natal and Post-Natal Child Physiology*, London, Longmans, Green & Company, 1920.
 100. COOK, H. W.: The clinical value of blood pressure determinations as a guide to stimulation in sick children, *Am. J. M. Sc.* 125: 433, 1903.

Chapter V

THE BLOOD

<i>Section 1</i> . . .	The Erythrocytes; Number and Development
<i>Section 2</i> . . .	The Erythrocytes; Hemoglobin Content and Other Characteristics
<i>Section 3</i> . . .	The White Blood Cells
<i>Section 4</i> . . .	Peculiarities of Blood Coagulation in Neonatal Life
<i>Section 5</i> . . .	Clinical Summary

THE ERYTHROCYTES: NUMBER AND DEVELOPMENT

TWO PROCESSES can be traced in the pre-natal morphology of the blood. One of these is the development of cells toward the objectives of extra-uterine physiology. The other consists of the temporary adaptations by which this preparation for life after birth is altered to meet the present exigencies of life before birth. Processes of the first type are those which tend to make the blood of the fetus increasingly similar to that of the extra-uterine organism; adaptations of the second sort generally tend to do the opposite and to make the fetal blood quite different from that of the extra-uterine subject.

During the earlier and embryonic phase of human intra-uterine life, the growth of red blood cells is largely a development of the first sort mentioned above, and the result differs from that observable during the later and fetal phase. Thus, in embryos of 26 and 28 mm., or at seven to ten weeks after conception, a mass of young cells is under formation and about a quarter of the red cells are nucleated. This relative maturation of the intra-vascular blood proceeds at such a rate that by about the fourth or fifth month (or in embryos of 146 to 170 mm.) nuclei are found in less than one per cent of the red cells.^{1,2} By this time the fetus seems to have arrived at a stage which will alter only quantitatively during the remaining half of gestational life, and much of this alteration consists of adaptation to the intra-uterine environment by activities which carry the fetal blood considerably beyond the mark established for the extra-uterine organism. The division of the long span of human fetal life into an early phase of development, fol-

lowed by a later one of increased intensity in the use (or adaptive over-use) of a relatively established pattern, suggests that man is born much later than are many other species. Human fetuses are given the last two months of intra-uterine life more for nurture than for the perfection of their organ systems, and are in some aspects warped away from the standard pattern by this extra post-developmental uterine sojourn.

Thus, some hematopoietic processes are maintained through late fetal life only to cease or to be much altered soon after birth, so that there are profound hematological differences between a nine months' fetus and a week old infant. Extravascular erythropoiesis in the liver could not be found by Gilmour¹ in infants more than five days old, and by the fifteenth day of life, according to that author, erythropoiesis occurs nowhere except in the marrow. Not only the sites but also the whole tempo of red cell and hemoglobin formation are certainly readjusted in neonatal life. Study of the sternal marrow at birth³ has revealed as many as 32 per cent of the total cells encountered to be erythroblasts or normoblasts. One week later this figure had fallen to about 12 per cent. Wintrobe and Schumacher^{4,5} have presented a few investigations of human fetal material together with a large mass of data from animal fetuses, all of which show the similar phenomena of progressive elevation in total red blood cell count and hemoglobin during the last half of fetal life. Obviously this mounting tide must ebb, or at least cease to rise, after birth.

The red blood cell count of the premature infant at birth should, according to these data, usually be expected to be less than that of the newborn, in contradiction to Feldman's statement⁶ that erythrocytes are more numerous in fetal blood than in postnatal life. That author quoted a report of Italian workers in 1899⁷ as having found as many as eight million red blood cells per cubic millimeter in the blood of an eight months' fetus. Slawik⁸ records slightly higher counts in nine premature than in eighty-two mature infants, but the figures are of doubtful statistical significance. If the fetus at seven or eight months is provided with more red cells than the baby at birth one might infer an oxygen lack which is greater at the earlier than at the later stage of development. There is no recent work to indicate that this is the usual relationship. On the other hand, the data available on this point and from counts themselves rather support the assumption that during late human fetal life the red cells are increasing toward but have not yet attained the level that will appear at full-term birth, just as is the case with fetal animals.

TABLE 17*

NUMBER OF ERYTHROCYTES (MILLIONS PER CU. MM.) IN THE BLOOD OF
NEWLY BORN INFANTS

Author	Year	No. Patients	Mean	Min.	Max.	Remarks
1. Lande ¹¹	1919	12	(4.65)	3.8	5.8	Average of 8 pre- mature and 4 ma- ture—first day
2. Lucas ¹²	1921	31	5.51	4.0	6.6	Cord tied late
3. Mayers ¹³	1922	41	7.63	5.06	9.61	
4. Lippmann ¹⁴	1924	41	5.19	4.12	6.44	Cord tied late
5. Silvette ¹⁵	1927	30	4.52	3.28	5.70	
6. Sanford ¹⁶	1928	200	5.8	4.2	8.0	
7. Forkner ¹⁷	1929	15	5.96	4.6	7.0	Living cells
8. Mitchell ¹⁸	1929	69	5.68	4.12	8.23	
9. Snelling ¹⁹	1933	20	6.20	4.70	7.90	
10. Gordon & Kemelhor ²⁰	1933	30	5.35	4.29	6.41	Second day
11. Merritt & Davidson ²¹	1933	71	5.95	4.60	6.80	
12. Merritt & Davidson ²²	1934	26	(5.54)			Premature infants
13. Mugrage & Andresen ²³	1936	40	4.9	4.1	5.7	Blood from cord during pulsation
14. Faxén ²⁴	1937	36	5.69	3.79	7.59	
15. Andersen & Ortmann ²⁵	1937	43	5.21	4.07	6.85	
16. Guest et al. ²⁶	1938	34	4.8	3.8	6.0	Samples from cord
17. Wollstein ²⁷	1939	25	4.8	4.0	5.5	Approximate fig- ures from graphs
18. DeMarsh, Alt, Windle ²⁸	1941					
A. Cord clamped early		25	5.57	4.2	6.7	Specimens from in- fants at 20–75 min. were higher than those from cord but lower than those later in first day.
B. Cord clamped late		25	5.99	4.7	7.6	
19. Chuinard, Osgood, Ellis ²⁹	1941	20	4.66			During first day; cord tied early

* Table modified from that of Andersen and Ortmann.²⁵

The difficulty is to place the human subject in proper comparison with the animal one. Windle⁹ has shown that cats, which have a gestation time of 67 days, produce an increasing number of erythrocytes not only steadily until birth, but also almost uninterruptedly for some time after, so that whereas their fetal red cell counts may have risen to five million per cubic millimeter at birth, they may have proceeded to eight million 70 days later. Other

workers¹⁰ have demonstrated a similar development of red blood cells in the pig. This animal, with 106 days of gestation, may have less than a million red blood cells per cubic mm. at 40 days of fetal life, three million at birth, four million a month later, and over six million in its adult life. One may think of the later months of gestation in the human as overlapping these early post-fetal phases of animal life, so that the human fetus is born during, or at the close of, a period of red blood cell and (probably) hemoglobin augmentation. Figures from premature infants are difficult to interpret unless they are from samples obtained almost as soon as the infant is born, because such complex changes occur in the early days after premature delivery. Only a few premature infants have been studied in this way. Data from two series appear in parentheses in Table 17 where they may be compared with figures from mature infants.

Lande's figures¹¹ which include premature infants, are lower than these usually observed in infants at full gestation. Merritt and Davidson's^{21, 22} work offers an opportunity of comparing data from prematures with a series of counts done by the same authors upon the blood of mature infants. While the difference between averages of 5.54 and 5.95 millions per cubic mm. is not great, the figure for premature infants is lower than that for mature ones, and is thus in keeping with the hypothesis that the human fetus is constantly adding to its store of red blood cells even until the end of intra-uterine existence. This is shown by the erythoblast levels during gestation and also by the oxygen-carrying capacity of blood from two prematures studied in another investigation.³⁰ Each of these infants (or fetuses) of 5 and 7 months' gestation had less capacity for oxygen transport per unit of blood, and less hemoglobin, than the average measurement for full-term infants in the same series.

The accompanying table of red blood cell counts for the earliest hours of life is by no means complete, but contains enough representative material from enough standard studies to illustrate one important observation. This, advanced especially by Andersen and Ortmann (from whose discussion the table was adapted), is that the content of erythrocytes in the blood at birth varies to an extraordinary degree. Andersen and Ortmann have calculated a coefficient of variation of 12.48 per cent for their data on the blood of 43 infants at birth, whereas in larger groups of adults this coefficient tends to be between 3.5 and 7 per cent. Thus, the infant begins life with a highly reactive bone marrow² and with a decidedly variable number of red blood cells, so variable in fact that an estimation of the total blood volume has been suggested as a

necessary piece of data before the significance of any individual red blood cell count at birth may be evaluated. Yet the wide range between minimum and maximum in any one observer's data from cord blood indicates that the number of red blood cells during early life must be actually and not merely relatively a variable figure.

A more obviously apparent and more widely known observation which appears in the table is that the number of red blood cells at birth is more or less above the normal for later life. If five million red blood cells per cubic millimeter be taken as an average figure for the adult populace, all but four of the sixteen mean values given for mature infants on the first day of life will be found to be that large, or larger. There is, however, so wide a zone of normal variation that normal values of four million or less may be expected to appear occasionally. In fact, attention may be called to the figures of recent workers, such as Guest and his colleagues,²⁶ and Wollstein,²⁷ in each of whose studies there was an average value of 4.8 million red blood cells per cubic mm. High red blood cell counts are not always characteristic of the blood at birth; variations in the red blood cell count are typical.

Reasons for the wide scattering of data might be sought in nationality, race or climate. That there could be variations as a result of such causes has been suggested in the early work of Schiff,³¹ and touched upon in the discussion of later authors.³² As responsible factors these seem hardly worthy of consideration when one compares the observations resulting in the highest values in Table 17 (Mayers, 1922) with those of DeMarsh, Alt and Windle in 1941. The latter results differ from the former ones by over 20 per cent, but both were obtained from patients at the Cook County Hospital in Chicago. The more recent figures from this institution do bring out one factor affecting the red blood cell and hemoglobin levels at birth and later in such a way as may explain a good many discrepancies between reported observations. This factor is the time at which the umbilical cord is clamped or tied. The work of the same investigators regarding blood and plasma volume differences depending upon the management of the cord has been commented upon in an earlier chapter. Apparently the omission of the placental blood from the circulation by early clamping alters the red blood cell count made during the first 70 minutes after birth by almost 10 per cent. The authors²⁸ present a table in their original article showing that a similar effect appears in the work of the few other observers who have mentioned the time of cord clamping. A more striking difference due to this factor was shown by red blood cell

counts made after one or two days of life. At one day the erythrocytes of infants whose cords were tied early had fallen from an average of 5.57 million to one of 5.47, whereas instead of falling the figure rose from 5.93 to 6.22 in the group allowed "to retrieve their placental blood." A more marked expression of this advantage to the latter group was shown by the amounts of hemoglobin, as will be mentioned below.

Not only may the management of the cord at birth influence the composition of blood in the earliest days of life; there is considerable evidence that capillary puncture yields blood with a higher cell count than venipuncture.³³ Moreover, a few hours' or a day's difference in the times at which blood samples are taken for study may also lead to a considerable variation. Most authors who have investigated the matter agree that more erythrocytes and more hemoglobin are present in the blood a few hours after birth than in that of the cord itself, and this rise continues through the first 24 hours, sometimes even longer. A difference in number of red blood cells as great as that between about 5.5 million at birth and 6.325 million at 24 hours has been reported in averages from 15 infants.³⁴ Such figures indicate that the time of sampling as well as the treatment of the pulsating cord must be consistent if figures are to be collected for the purpose of comparing normal values. The immediately post-natal increase in erythrocytes apparently occurs because of continuing erythropoiesis.

After the first day of life, and until the sixth to ninth week the number of erythrocytes per unit of blood tends to fall, but more gradually at first than is often believed. Wollstein²⁷ found the number late in the first week still above that at birth, and at two weeks of age scarcely below the birth figure; and Guest's value of 5.7 million per cubic mm. as average at one day may be compared with 5.12 at seven days. After about 14 days the decrease in erythrocytes progresses somewhat more rapidly, so that by a month their number has fallen to three or four million, with a persistence of extremely wide variation encountered. Washburn,³⁵ who has been especially interested in this, has suggested its explanation in terms of the variables introduced by changes both of total body mass and blood production as reflected by the numbers of reticulocytes.

Erythroblasts and reticulocytes are both found fairly frequently on the first day of life. An average of about seven nucleated red blood cells occurs for each 100 white blood cells in the cord blood,² and one to two per hundred white blood cells may be encountered during the first day,³⁶ so that Lippmann's¹⁴ maximal figure of 37 erythroblasts to 100 white blood cells must have occurred in a very

exceptional newborn infant. Agress and Downey³⁷ found one normal infant aged one hour to have blood with 13.5 nucleated red cells per 100 white blood cells, which is about as high as can safely be considered normal in view of Anderson's recent and painstaking review of the subject.² A universal finding is that the number of nucleated cells declines immediately after birth, so that by the fifth day Lippmann could find only a maximum of 0.2 erythroblasts per 100 nucleated cells. Josephs³⁸ quotes a number of references to show that five or six per cent of the red blood cells are reticulocytes at birth. This percentage also falls immediately (or after a very transient rise) to reach less than half of one per cent by the eighth to tenth day.^{27,39}

All of the following evidence would lead one to expect an increased fragility of the red blood cells at or soon after birth. Immature cells are known to be present in abnormal numbers and then to disappear rapidly; the total erythrocyte count per unit of blood is elevated at first and gradually falls; while so much bilirubin accumulates in the blood during this time as to suggest an even more rapid fall of the erythrocytes than their enumeration shows. Finally, one of the annoyances of handling umbilical cord blood in the laboratory is its obvious tendency to become hemolyzed, so that extra care must be used if one wishes to secure a clear serum. What is the actual red blood cell fragility in neonatal life? It is not for lack of observations that the answer must be a disappointingly guarded one. Waugh, Merchant, and Maughan³² have reviewed a literature which covers between 15 and 20 studies: from a slight majority of these the conclusion has been drawn that, instead of an increased fragility, there is an increased resistance to anisotonic salt solutions at and after birth, as compared with the normal behavior of adult red blood cells. In five researches no difference from the adult was noted. The same authors describe an investigation of their own in which the fragility was shown at birth to be the same as that of the adult's erythrocytes, became slightly less during the next four days, and then returned to the normal adult level. At no time during the first nine days of life (in about 220 observations on 65 infants) was a diminished resistance of the blood cells observed, nor could anything be elucidated further as to neonatal peculiarities except the presence of anisohemolysis, which is described as "an abnormal spread in the dilutions at which they hemolyze, so that one finds a certain number of cells which are unusually resistant and others which are abnormally fragile." However they react to saline or to other testing solutions,⁴⁰ the erythrocytes of the newborn are subject to excessive hemolysis on

standing in their own plasma, and do go through an unquestionable period of considerable destruction.

THE ERYTHROCYTES: HEMOGLOBIN CONTENT AND OTHER CHARACTERISTICS

To a certain degree the quantitative changes in the number of red blood cells during the first days of life are reflected also in the amount of hemoglobin per unit of blood. Unfortunately it is impossible to make exact statements and it is surprisingly difficult to give entirely satisfactory normal values, since measurements of hemoglobin have been performed by such different techniques and recorded by such varying standards that no large group of comparable figures can be assembled for purposes of averaging. The suitability of hemoglobin measurements for comparison is of course also affected by all the factors of time and source of sampling and type of delivery, the effect of which upon erythrocyte counts has been discussed.

In general it is true that the blood is richer in hemoglobin at birth than at later periods, and that the amount rises in the first few hours and then falls rather gradually until about the end of the second week, when it falls more rapidly, so that by two to three months of life the infant is normally or "physiologically" anemic. Kato and Emery⁴³ have carefully studied a large number of infants and found a mean value of 18 grams of hemoglobin per 100 cc. of blood at birth, 19.7 grams at 9-12 hours, 17.7 in the second week, and only 10.6 at the second month. With a different technique but equal care Faxén²⁴ found 23.2 grams on the first day, 21.7 the seventh, and less than 18 grams at one month. All of the other more recent investigations have resulted in lower values. Thus in 20 infants (whose cords had been tied early at birth), Chuinard and his colleagues²⁹ found during the first day an average of 17.2 grams. Still lower figures are those of Waugh and others³² who used an Evelyn photocolormeter to measure the hemoglobin in samples from 52 newborn infants. The cords of these subjects were not clamped until after pulsation had ceased, and the infants were thus not unduly deprived of blood; nevertheless the mean hemoglobin value at birth was only 15.4 grams (extremes 11.8 to 18.4) with a slight rise thereafter and a decrease to 14.7 grams on the ninth day. Since these authors take 15.6 gm. per 100 cc. as the value arbitrarily representing 100 per cent of normal, their work indicates that the majority of newborn infants, at least in Montreal, have blood with no more hemoglobin than should be expected in that of a normal adult. The recent data of DeMarsh and others^{28, a} from Chicago were obtained with a Hellige type of apparatus,

checked by measurements of oxygen capacity. The infants reported were treated in the same manner as the subjects of Waugh's research. Yet as compared with the Montreal series whose average hemoglobin level at birth was 15.4 grams, the average of the Chicago series was 21.6 grams. This is more than 40 per cent greater than the other average. The subsequent behavior of hemoglobin levels followed much the same pattern in the two groups from day to day, but the actual values are so widely separated as to indicate why it is that a standard "normal" hemoglobin value for American infants cannot yet be stated. Perhaps there may be no universally acceptable figure.

The size and the volume of erythrocytes at birth are quite well established upon the observations of several workers who agree that although the cells exhibit a considerable variation in size those of larger diameter predominate. This macrocytosis is carried over from fetal life, for during that period the average red blood cell is even larger in diameter than at birth. Guest and his colleagues²⁶ found the mean red blood cell volume at four years to be 80 cubic microns, at one year 71 cubic microns, at ten days 107 cubic microns, and in cord blood 113 cubic microns. According to some authors the anisocytosis of neonatal life is of comparatively short duration and disappears by two weeks of age, even though the actual number of cells and the amount of hemoglobin per unit of blood still remain spread over a wide range of normal. The most recent determinations,^{23,26} however, show scarcely less scatter of red cell size at two months than at birth. The size of the average red blood cell does diminish, probably from birth, as Guest's group has shown very clearly in diagrams comparing blood from the cord with that obtained one to ten days later. Because both cell size and number decrease, either from birth or from a point during the first day of life, the volume of packed cells (hematocrit) declines fairly consistently from an early peak, which Mugrage and Andresen²³ found to average 53.18 cc./100 to a low level of 34.18 cc. at from two to four months. Expected normal variation in this figure at birth is perhaps twice as great as at five years; while during the period from three days to two months the normal variation may be even four or five times that to be expected in later childhood. The hematocrits in the Montreal series³² were not so high (51.3 per cent) at birth; those in Copenhagen infants²⁵ averaged 56.5 cc. or slightly higher.

The mean corpuscular hemoglobin is probably correctly stated as about 35 to 37 micromicrograms of hemoglobin per single red blood cell at birth, Faxén's²⁴ value of 40 to 41 micromicrograms

being based on a hemoglobin level as high as 23.6 grams per 100 cc. in the first days of life. The agreement of American workers upon a figure of about 33 to 37 has been reasonably close.^{23,44} The mean corpuscular hemoglobin content falls, with or without a brief pause at the cord blood level, during the first 24 hours; the rate and degree of this fall is roughly proportionate to the curve of red blood cell size, so that the mean of hemoglobin concentration in a given mass of red blood cells (an expression of the "color index") tends to remain fairly constant between birth and perhaps five to six months, even rising slightly in the first days and months of life. Guest thought that these findings gave evidence of new and smaller cells, in which the concentration of hemoglobin was higher, entering the circulation at this time. That excessive erythropoiesis is going on in the marrow during the first day or two of life and that it decreases rapidly thereafter is shown by other observations.^{17,37} The argument of earlier authors that the red blood cell and hemoglobin increase after birth may be brought about simply by dehydration and concentration of the blood can be answered also by Forkner's observation that the curve of serum protein concentration does not parallel that of red blood cell concentration.

Any *summary* of the changes in erythrocytes and hemoglobin following birth must begin by emphasizing the wide limits of variation observed in the blood of normal infants. Generally, both cells and hemoglobin are above the usual adult values at birth, and in that respect occupy a situation which has been increasingly attained during the later months of gestation. This gestational overgrowth appears to continue for a few hours after the severance of the cord; there may also be a brief effect of hemoconcentration here from loss of body fluid. Erythroblasts and other immature cells are, as might be expected, found in unusual profusion during the first day, but their decrease is then rapid, although the number of red blood cells and the amount of hemoglobin fall only gradually until an age of about two weeks and then more precipitously. The characteristic erythrocyte at birth is a large cell, although subject to wide normal variation. The size soon decreases, this qualitative change taking place more appreciably than the quantitative diminution in number of cells. The hematocrit value of 50 to 55 at birth is subject to a parallel decrease. At two weeks the blood of the infant is scarcely less polycythemic than was that in the cord at birth, nor is the amount of hemoglobin per mass of packed cells appreciably diminished, but the cells themselves are smaller and individually unable to carry as much hemoglobin as the earlier erythrocytes. The cell wall at birth is not deficient in resistance

when tested by exposure to anisotonic salt solutions; nevertheless it breaks easily when preserved in its own plasma, so that some form of increased fragility must be ascribed to it.

THE WHITE BLOOD CELLS

To describe in mathematical detail the inter-relationships of the various white blood cells immediately after birth would require a long discussion. So well has the subject been reviewed by Wollstein,²⁷ Lippmann,¹⁴ Lucas,¹² Forkner,¹⁷ and most recently Washburn⁴⁵ that an exact account is perhaps unnecessary; indeed a detailed tabulation might be more confusing than valuable so wide is the latitude of normal variation. Washburn^{42,a} for example, came to the conclusion that the total white cell count of infants aged between one and sixteen weeks might vary from four thousand to twenty-three thousand per cubic mm. without indicating the presence of any demonstrable disease process. He could find no evidence of orderly rhythm in fluctuations of leucocyte counts during the hours of day or night, nor any correlation between the number of white cells and such factors as the intake of food, the processes of digestion, bodily activity or minor external disturbances. All this evidence of uncontrolled and unpredictable swing in numbers makes one hesitant to outline a rigid pattern for the "normal" total or differential count at birth or shortly after birth, or to suggest that quite startling departures from such a pattern must mean a significant abnormality.

Nevertheless, in a general way the total white blood cell count at birth may safely be described as elevated, the elevation being largely made up of polymorphonuclear leucocytes, a high percentage of which are young forms. Lippmann¹⁴ observed that the peak value in the total white cell count occurred at 12 hours after birth. Kato⁴⁶ placed it at 24 hours. Wollstein,²⁷ on the other hand, found that a decline began immediately after birth. The cells are immature; a few that contribute to the increased white blood count during the first days of life are myelocytes; Kato mentions leukoblasts. By about the fourth day the leukocytosis of the first few hours has sharply diminished, largely by virtue of a rapid decrease in the number of circulating polymorphonuclear neutrophils. All of this is easily seen in Table 18, a condensation of Forkner's chart¹⁷ from the bloods of 15 infants, which is reproduced as being fairly representative. The table shows that from a normal range of 15,000 to 45,000 white blood cells per cubic mm. on the first day, the extremes fall to 4000 and 18,000 on the fourth. These must be taken as illustrative, not absolute, values. It will be noted, and

TABLE 18
(SUMMARIZED FROM FORKNER'S DATA¹⁷)

No. Cases	Age	Absolute Number per cu. mm., and per cent of White Blood Cells •											
		Total White Blood Cells		Neutrophils		Eosinophils		Monocytes		Lymphocytes		Neutrophilic Myelocytes	
		#	%	#	%	#	%	#	%	#	%	#	%
13	1st day												
	Maximum*	45,000	82.5	33,525	5.5	895	11.5	5175	36.0	8722	10.0	1908	
	Minimum*	15,250	53.0	8,628	0.0	0	3.0	696	9.0	2000	0.0	0	
	Ave.—1st day	24,945	68.7	17,458	2.1	429	6.5	1674	18.3	4338	3.6	860	0.8
9	3, 4, 5 days												
	Maximum*	18,800	59.0	10,152	13.0	1110	23.0	4324	44.5	5184	1.5	174	
	Minimum*	4,000	32.0	1,800	1.5	168	10.0	920	15.0	600	0.0	0	
	Ave.—3, 4, 5 days	10,636	45.2	4,927	6.5	600	16.9	1803	29.6	3120	0.55	60	1.3
10	6, 7, 8 days												
	Maximum*	16,400	67.0	8,528	7.0	727	19.5	2362	61.0	7015	3.0	437	
	Minimum*	7,600	26.5	2,156	1.5	160	7.0	762	17.0	1292	0.0	0	
	Ave.—6, 7, 8 days	10,385	39.25	4,094	4.0	411	14.3	1450	40.75	4251	1.0	103	0.8
10	9, 10, 11 days												
	Maximum*	16,500	46.0	6,141	6.5	873	28.0	3738	69.0	9453	1.0	102	
	Minimum*	8,100	18.5	1,976	1.5	205	8.5	1164	22.0	2937	0.0	0	
	Ave.—9, 10, 11 days	12,821	28.9	3,760	3.4	417	17.1	2224	49.15	6244	0.2	24	1.2

* Note—The maximum and the minimum per cent and absolute numbers occasionally represent samples from different infants.

this is a third generally proven observation, that as the number of polymorphonuclear cells declines the number of lymphocytes (which may have suffered an early decline also) begins to increase, and by the sixth to eighth day is as great as, or greater than, the number of polymorphonuclear cells. Agress and Downey³⁷ report evidences of obvious lymphocytic production from reticulo-endothelium between the seventh and eleventh days of life, whereas this feature was not found by them in the blood of babies during the first two days. Washburn^{42,a} has shown that one week after birth the pronounced variations in total white cell count tend usually to be caused by changes in the lymphocyte portion, whereas before the numbers of leukocytes and lymphocytes become equal, or roughly, during the first week of life, the leukocyte fraction determines the fluctuations of total figures.¹⁴ Eosinophils and basophils may occur in the blood smears of earliest infancy in about the proportions represented by these cells in later life. To plot any sort of characteristic curve for them seems unjustifiable. On the other hand, the occasional rise of monocytes in the second week of life to levels as high as 17 per cent is worthy of remark. A sharp drop in the number of these cells occurs thereafter.

The few available studies of premature infants indicate that: (1) there may be a larger proportion of immature white cells of all forms in the circulating blood; (2) the total number of white cells, varied as it may be, is usually lower than that found at full term birth, averaging 7500 cells per cubic mm. in ten infants examined by Lichtenstein⁴⁷ on the first day; and (3) the adjustment by which lymphocytes begin to outnumber polymorphonuclear cells at eight to ten days of normal neonatal life may be somewhat further delayed after premature birth.²⁷

It would be foolish to attempt a physiological explanation of the kaleidoscopic relationships and changes which have been described. The factor of relative anoxemia which has been so widely used to explain high red blood cell and hemoglobin values at birth probably cannot be applied to the peculiarities of the white blood cells. During exposure of adults to high altitudes, whether of life-long or only brief duration,^{48,49} leukocyte and lymphocyte proportions have been shown to remain fairly steady. Neonatal variations in the number of any one type of cells are not such as to suggest a particularly erratic performance in either production or destruction of that individual cell series; indeed, unpredictable reactions by various cell types to minor stimuli such as transient infections are the mark of the white blood cells throughout infancy. Certainly a general white blood cell increase in the few hours after birth may to

some extent be the result of dehydration, but the presence of a polymorphonuclear leukocytosis in blood taken within five minutes after delivery can hardly have come about in that way. Kato⁴⁶ suggests that this "granulocytosis closely resembles the blood pictures of acute infections in older children, and may reflect rapid, temporary adjustment of the defense mechanism, upon sudden transition from sterile intra-uterine life." Various forms of shock which might be compared to that undergone by the infant in being born do not produce simple leukocytosis in the blood of experimental animals, or, rather, a leukocytosis may be produced but only secondarily to a leukopenia.⁵⁰ Since there is no clear-cut leukopenia in the newly born the leukocytic picture in neonatal life cannot as yet be explained as due to the physical shock of birth. Moreover, Lippmann¹⁴ analyzed his counts of the white blood cells with reference to any correlation between unusually traumatic deliveries and outstanding aberrations in the leukocyte picture, with completely negative results.

Perhaps the most useful conclusion that can be drawn from this evidence is that one should be very hesitant to apply testimony from the white blood cell count to any clinical problem occurring in newborn life.

PECULIARITIES OF BLOOD COAGULATION IN NEONATAL LIFE

It is, as with other elements, impossible to set the exact normal levels for blood platelets at birth or thereafter, or to postulate a process of formation which fits a particular theory. Baar and Stransky⁵¹ could only state that a variability of platelet size with a general tendency to enlargement, was found in the newborn period.

Reviews of the subject since that time have added a few further observations. In 1933 Merritt and Davidson²¹ published a group of counts, part of which are included in the table given below. Characteristic of this material was a fairly regular rise both in minimum and maximum values, from birth, so that by the third month the mean of 58 counts was 348 thousand platelets per cubic mm. as compared with 220 thousand at delivery. In some of a small group of premature infants McLean and others⁵² have found the number of platelets to be below that for infants at term, so that a general tendency for platelet increase appears to start before birth and continue afterwards. Platelet counts recently published by Hurwitz, Mulay, and Lazarus,⁴⁴ although in the general range of the table given, do not show the same gradual elevation with age;

however, the number of infants is small, and the series only covers thirteen days of life. Wollstein and Kreidel,²⁷ working at the same clinic from which the figures of Merritt and Davidson were obtained, found average platelet values of over 300 thousand per cubic mm. of blood at birth, and a rise thereafter to as high as 609 thousand on the seventh and 744 thousand on the fifteenth day. These might be within the range of occasional observations; it is difficult to understand them as averages, so much higher are they than those in the accompanying table. Moreover, Leslie and Sanford⁵³ have found a fairly constant figure of 500 thousand to 600 thousand platelets per cubic mm. of plasma in the first ten days of life. The figure for the whole blood, since its volume is perhaps twice as great as that of the plasma, would according to these

TABLE 19
PLATELETS IN THE BLOOD OF NORMAL INFANTS
(from Merritt and Davidson²¹)

Age	No. of Observa- tions	Platelets—Thousands			Stand- ard Dev.	Coeff. of Vari- ation
		Min.	Max.	Mean		
Birth—Cord Blood	73	140	290	227	39	17
1 week—Capillary Blood	69	160	320	233	45	19
2 weeks—Capillary Blood	19	170	370	242	50	21
3 weeks—Capillary blood	23	160	380	269	62	23
1 month—Capillary Blood	48	200	370	277	51	18
2 months—Capillary Blood	59	200	470	320	67	21
3 months—Capillary Blood	58	200	480	348	64	18

counts be some 250 to 300 thousand platelets per cubic mm. The same authors have also put forward the view that the platelets of the newborn are more resistant to disintegration than in the case later in life, but this awaits confirmation. Arneth,⁵⁴ on perhaps debatable evidence, has come to the reverse conclusion, and believes the platelet picture from the second week on to be quantitatively and qualitatively favorable for clotting of the infant's blood. Thus there seems to be no serious thrombocytopenia at delivery or after. But several times an interlude of slight decline has been observed at about the third to sixth day^{27, 53} which would suggest a possible relationship to clinically evident alterations in coagulation.

Because of the frequency of so-called hemorrhagic disease during the first week, and particularly since the recent knowledge of the substance called vitamin K has become available, the phenomena of blood clotting in neonatal life have been much studied. In gen-

eral it may be said at once that although there may be notable delays in blood clotting, a quantitative or qualitative neonatal deficiency in platelets cannot be blamed for them. The bleeding time of the infant has been sufficiently investigated to show that it is consistently two or three minutes at birth and increases to four or perhaps five minutes soon thereafter,^{21,55} but the clotting time is subject to much greater variation, and may be as long as eleven or twelve minutes, even in babies who show no sign of hemorrhage.^{*56,57} There seems little doubt that these changes in clotting time are the result of alterations in the blood as to its prothrombin content. Since this substance is usually measured in units of time required for conversion into thrombin, its deficiency is often referred to as an increase in prothrombin time. The prolonged clotting time so frequently occurring in the newborn is almost uniformly accompanied by, and in the vast majority of instances probably the result of hypoprothrombinemia or deficiency in "available prothrombin,"⁵⁸ and a prolonged prothrombin time. When this condition involves actual bleeding, as from the cord, beneath the skin, into a viscus, or elsewhere, the clinical picture is that called hemorrhagic disease.

A considerable literature has sprung up from the rapid cultivation of this field of medicine, and no attempt is here made to review it completely. Several of the important contributions are listed in the bibliography.⁵⁷⁻⁶³ Their purport is that the usual neonatal decrease in the prothrombin value—and thus increase in the clotting time—tends to be most marked on the third or fourth day, following which it rather rapidly approaches the normal figure for adult life, attaining that level by the seventh to tenth day. On the other hand, the maternal prothrombin values at and after the infant's birth are not decreased but tend to increase,⁶⁴ nor do they in any consistent way parallel or reflect the figures for individual infants. Dam and Schönheyder⁵⁹ discovered in 1935, and called vitamin K, the anti-hemorrhagic factor which was later shown to be deficient in the blood of newborn infants. The response to the administration of this substance, or to one of the similar synthetic preparations such as 2-methyl-1, 4-naphthoquinone, is an almost immediate increase in the prothrombin level. When the factor is given to the mother just before or at delivery, it causes an elevation of her already normal prothrombin value. A parallel effect is noted in the

* Actually coagulation times as long as 15 minutes have been published by Lucas and his colleagues¹² as normal for infants on the day of birth, but these were from sinus blood, and samples from venous sources require a much longer time for clotting than do capillary specimens.

blood of her baby, so that the obstetrical use of vitamin K practically prevents hypoprothrombinemia (and its tendency to bleeding) either at birth or in the critical few days thereafter.

Exactly how the presence of vitamin K in the body produces its effect upon prothrombin is not known, but there are interesting speculations as to why the infant comes to be deficient in the former substance. It is probable that at birth the fetus is provided with sufficient vitamin K from the normal maternal supply, but as soon as this is utilized some other source is necessary. The adult appears to absorb vitamin K from the gastro-intestinal tract, a proper amount of bile and normal absorptive powers supposedly being essential to the process, as well as the presence of a supply of vitamin K either directly from the diet or from the action of bacteria upon certain foods. The normal functioning of the liver and of the intestinal wall may well be disturbed in early life, but a more obvious fault may be the lack of enough intestinal bacteria, if not also of food upon which more organisms might act. The suggestion has been offered by Salomonsen and Nygaard⁶⁵ that the early feeding of raw rather than pasteurized cow's milk is useful for seeding the intestinal tract with bacteria necessary for this process. Yet Sanford and Shmigelsky⁶⁶ have shown that normal prothrombin values could occur in the blood of an infant in whom the presence of food or of bile in the bowel was prevented by congenital abnormalities.

As yet it has not been ascertained whether premature infants become more deficient in prothrombin than do those born at full gestation. Kato and Poncher⁶⁰ have found that no correlation exists between birth weight (above 1 kilogram) and prothrombin time during the first day, as might be expected since it is probably the transmitted maternal supplies which are then represented. These authors observed that the blood of premature infants showed characteristically wider fluctuations in prothrombin time during the succeeding days than did that of mature infants of the same age. But Waddell and Lawson⁶⁷ (although in a smaller number of patients) found the reverse to be true, their premature infants developing less marked aberrations of prothrombin time on the second to fifth days than did a comparable series of babies born at term. It would be interesting to know whether the same feeding and nursery techniques were used in both groups of subjects.

Attention to prothrombin has overshadowed that devoted to other participants in blood clotting, but a few measurements of fibrinogen have been made, all of which show a neonatal value within normal limits as compared to an elevation in the maternal blood. Differences of method account for differences in absolute

quantities recorded. According to Nevinny⁶⁸ the blood of the average mother contains 0.38 gm. and that of the umbilical vein 0.24 gm. of this substance per 100 cc. Two recent studies^{69,70} indicate that the maternal blood contains about 0.5 gm. fibrinogen, the infant's blood between 0.25 and 0.35 gm. per 100 cc. of plasma. The actual weight of fibrin extractable from a unit of blood on the first day of life is about three-quarters of that found on the fourth to tenth day.⁷¹ Thus, although the clotting mechanism and the availability of prothrombin are disturbed during the course of the first days of life, the amount of available fibrinogen appears to be simultaneously increasing, a further proof that hemorrhagic tendencies at this time are rarely to be traced to fibrinogen abnormalities.

Contrary to the usually accepted theory that the rate of red cell sedimentation varies directly with the amount of fibrinogen present, the sedimentation time in cord blood is greatly prolonged whereas the fibrinogen at birth is only slightly depressed. By the Linzenmeier method, the sedimentation time is about $1\frac{1}{4}$ hours for infants aged two to twenty-four months, but in the blood of twelve infants during the first day the time has been found to be as long as 106 hours.⁴⁴ This is far beyond the proportions of the mild depression of fibrinogen level. In a series of infants studied by the author with McKhann and others⁷² there was no correlation between individual fibrinogen and sedimentation measurements. The fibrinogen was usually slightly lower than the adult amount, while sedimentation was always extremely slow, in sharp contrast to the behavior of maternal blood whose red blood cells during and immediately after pregnancy undergo sedimentation with unusual rapidity. An explanation of the slow sedimentation rate at birth cannot be in terms of fibrinogen content, and should in some way account for a comparatively large increase in sedimentation speed occurring by the second day of life. No theory which fits with these facts has yet been brought forward.

CLINICAL SUMMARY

The physician will usually wish information about neonatal blood as a means of deciding whether data from a given patient fall within normal hematological bounds. That these are very wide will be seen in Tables 17 and 18, for red and white blood cells respectively. In general, the concentration of erythrocytes is on the increase at birth and has reached a point, usually, though not always, above the adult number; at premature birth the figure tends to be slightly less. During the first day after full-term delivery the red blood cell count usually rises somewhat above that immediately

after birth. This is particularly true of infants who have been allowed to regain their placental blood. Immature erythrocytes should normally appear in decreasing number after extra-uterine life begins, though as many as 10 erythroblasts per 100 nucleated cells may normally be present at delivery and a reticulocytosis of 5 or 6% is characteristic at that time. In spite of the fact that the erythrocyte count normally displays a definite decrease by the second week as though cells were being removed from the circulation, no abnormal erythrocyte fragility has been shown to occur in neonatal blood.

A normal figure for hemoglobin concentration cannot be stated. In general the value tends to be above that for the adult, both because there are usually more erythrocytes in the blood at birth and because they tend individually to be macrocytic. A decline in cell size sets in almost at once, with a parallel decrease in the mean corpuscular hemoglobin, so that the color index may be expected to remain constant. The hematocrit undergoes a definite fall from the normal level of 50 to 55 at birth, because of the increased proportion of smaller cells.

The infant is born with a polymorphonuclear leucocytosis which may reach as high as 45,000 white blood cells per cubic mm. on the first day. A latitude of normal range probably unmatched at any other period of life is the outstanding feature thereafter, but through this two general processes are visible. One is a rapid fall in total count, the other a progressive rise in lymphocytes. By seven days of age, the infant usually has about half as many circulating white blood cells as at birth, the largest single component then being lymphocytic. A tendency for elevation of monocytes is also notable. In premature babies, the total white blood cell counts are usually somewhat below those of full-term ones, and the lymphocyte increase may appear a little less promptly after birth. In general, the formation of all of these cells appears to be under such loose control that diagnostic application of white blood cell counts calls for great caution at this time of life.

Although no consistent abnormality of platelets nor serious disturbance of bleeding time is present, coagulation has definite peculiarities. The clotting time and, more specifically, the prothrombin time, are slightly increased at birth but undergo a further and considerable increase during the second to fourth days after birth. Prevention of this hypoprothrombinemia (and the occasional associated hemorrhagic disease) should be accomplished by the administration of 2-4 mgm. of Vitamin K to the parturient mother or 1 to 2 mgm. to the newborn infant.

The other substances entering into blood coagulation are only moderately altered during the neonatal period. The blood at this age contains almost as much fibrinogen as that of the mother. Although fibrinogen content and sedimentation speed of erythrocytes are generally supposed to be directly related, the infant's fibrinogen level is only slightly reduced whereas the sedimentation rate is extremely prolonged in the neonatal period.

BIBLIOGRAPHY

1. GILMOUR, J. R.: Normal haemopoiesis in intrauterine and neonatal life, *J. Path. & Bact.* 52: 25, 1941.
2. ANDERSON, G. W.: Studies on nucleated red cell count in chorionic capillaries and cord blood of various ages of pregnancy, *Am. J. Obst. & Gynec.* 42: 1, 1941.
3. SHAPIRO, L. M., and BASSEN, F. A.: Sternal marrow changes during first week of life . . . *Am. J. M. Sc.* 202: 341, 1941.
4. WINTROBE, M. M., and SHUMACKER, H. B., JR.: Comparison of hematopoiesis in fetus and during recovery from pernicious anemia, together with consideration of relationship of fetal hematopoiesis to macrocytic anemia of pregnancy and anemia in infants, *J. Clin. Investigation* 14: 837, 1935.
5. WINTROBE, M. M., and SHUMACKER, H. B., JR.: Erythrocyte studies in mammalian fetus and newborn . . . *Am. J. Anat.* 58: 313, 1936.
6. FELDMAN, W. M.: *The Principles of Ante-Natal and Post-Natal Child Physiology*, Pure and Applied, London, Longmans, Green & Co., 1920.
7. BIDONE, E., and GARDINI, P. L.: Les hématies et l'hémoglobine de la femme grosse et du fœtus, *Arch. Ital. de Biol.* 32: 36, 1899.
8. SLAWIK, E.: Studien über die physiologischen Verhältnisse des Blutes beim Neugeborenen mit besonderer Berücksichtigung der Blutplättchen, *Ztschr. f. Kinderh.*, 25: 212, 1920,
9. WINDLE, W. F.: *Physiology of the Fetus: Origin and Extent of Function in Prenatal Life*. Philadelphia, W. B. Saunders, 1940.
10. JONES, J. M., SHIPP, M. E., and GONDER, T. A., JR.: Changes occurring in blood picture during fetal life, *Proc. Soc. Exper. Biol. & Med.* 34: 873, 1936.
11. LANDÉ, L.: Beitrag zur Hämatologie, Aetiologie und Therapie der Frühgeburtsanämie, *Ztschr. f. Kinderh.* 22: 295, 1919.
12. LUCAS, W. P. DEARING B. F.; HOOBLER, H. R. and others: Blood studies in the newborn . . . *Am. J. Dis. Child.* 22: 525, 1922.
13. MAYERS, L. H.: Study of the erythrocyte curve at various ages and its relationship to hemoglobin curve, *Arch. Int. Med.* 30: 478, 1922.
14. LIPPMAN, H. S.: A morphologic and quantitative study of the blood corpuscles in the new-born period, *Am. J. Dis. Child.* 27: 473, 1924.
15. SILVETTE, H.: Study of erythrocyte diameters in newborn, *J. Lab. & Clin. Med.* 13: 245, 1927.
16. SANFORD, H. N.: Effect of ultra-violet light on the blood of newborn infants, *Am. J. Dis. Child.* 35: 9, 1928.

17. FORKNER, C. E.: Studies on living blood cells of newborn. *Bull. Johns Hopkins Hosp.* 45: 75, 1929.
18. MITCHELL, J. M.: Relationship of jaundice and weight to blood values in newborn infant, *Am. J. Dis. Child.* 38: 518, 1929.
19. SNELLING, C. E.: Icterus neonatorum, *J. Pediat.* 2: 399, 1933.
20. GORDON, M. B., and KEMELHOR, M. C.: Icterus neonatorum; a study of the icterus index in relation to the fragility, hemoglobin content, and number of red blood cells, *J. Pediat.* 2: 685, 1933.
21. MERRITT, K. K., and DAVIDSON, L. T.: Blood during first year of life . . . *Am. J. Dis. Child.* 46: 990, 1933.
22. MERRITT, K. K., and DAVIDSON, L. T.: Blood during first year of life; anemia of prematurity, *Am. J. Dis. Child.* 47: 261, 1934.
23. MUGRAGE, E. R., and ANDRESEN, M. I.: Values for red blood cells of average infants and children, *Am. J. Dis. Child.* 51: 775, 1936.
24. FAXÉN, N.: Red blood picture in healthy infants, *Acta Paediat.* (Suppl. 1) 19: 1, 1937.
25. ANDERSEN, B., and ORTMANN, G.: On number of erythrocytes and content of haemoglobin in blood of new-born children, *Acta Med. Scandinav.* 93: 410, 1937.
26. GUEST, G. M., BROWN, E. W., and WING, M.: Erythrocytes and hemoglobin of blood in infancy and in childhood . . . *Am. J. Dis. Child.* 56: 529, 1938.
27. WOLLSTEIN, M.: Normal blood in infants and children, in *Handbook of Hematology*, Edited by Hal Downey, Vol. 2, New York, Paul B. Hoeber, 1938.
28. (a) DeMARSH, Q. B., ALT, H. L., and WINDLE, W. F.: Effect of depriving infant of its placental blood on blood picture during first week of life, *J. A. M. A.* 116: 2568, 1941.
- (b) WILSON, E. E., WINDLE, W. F., and ALT, H. L.: Deprivation of placental blood as cause of iron deficiency in infants, *Am. J. Dis. Child.* 62: 320, 1941.
29. CHUINARD, E. G., OSGOOD, E. E., and ELLIS, D. M.: Hematologic standards for healthy newborn infants . . . *Am. J. Dis. Child.* 62: 1188, 1941.
30. DARLING, R. C., SMITH, C. A., ASMUSSEN, E., and COHEN, F. M.: Some properties of human fetal and maternal blood, *J. Clin. Investigation* 20: 739, 1941.
31. SCHIFF, E.: Neuere Beiträge zur Haematologie der Neugeborenen, *Jahrb. f. Kinderh.* 54: 172, 1901.
32. WAUGH, T. R., MERCHANT, F. T. and MAUGHAN, G. B.: Blood studies on newborn . . . *Am. J. M. Sc.* 198: 646, 1939.
33. SACHS, A., LEVINE, V. E., GRIFFITH, W. D., and HANSEN, C. H.: Copper and iron in human blood; comparison of maternal and fetal blood after normal delivery and after Cesarean section, *Am. J. Dis. Child.* 56: 787, 1938.
34. RASI, F., and CELLEGHIN, O.: I globuli bianchi nel neonato, *Riv. di clin. pediat.* 37: 711, 1939.
35. WASHBURN, A. H.: Blood cells in healthy young infants; postnatal readjustments of red blood cells in individual babies, *Am. J. Dis. Child.* 62: 530, 1941.
36. SCHWARTZ, P., and BÜNGELER, W.: Die Geburtskrise des Blutbildes bei Neugeborenen, *Frankfurt. Ztschr. f. Path.* 35: 165, 1927.
37. AGRESS, H., and DOWNEY, H.: Blood picture of human newborns, with special reference to

- lymphocytes, *Folia haemat.* 55: 207, 1936.
38. JOSEPHS, H. W.: Anaemia of infancy and early childhood, *Medicine* 15: 307, 1936.
 39. KATO, K.: Physiological variations of reticulocytes in newborn; study of 219 cases, *Folia haemat.* 46: 377, 1932.
 40. WAUGH, T. R., MERCHANT, F. T., and MAUGHAN, G. B.: Blood studies on newborn . . . *Am. J. M. Sc.* 199: 9, 1940.
 41. GOLDBLOOM, A., and GOTTLIEB, R.: Icterus neonatorum, *Am. J. Dis. Child.* 38: 57, 1929.
 42. BONAR, B. E.: Icterus index in new-born infant, *Am. J. Dis. Child.* 50: 1143, 1935.
 43. KATO, K., and EMERY, O. J.: Hemoglobin content of the blood in infancy . . . *Folia haemat.* 49: 106, 1933.
 44. HURWITZ, S., MULAY, A. S., and LAZARUS, D. S.: Sedimentation time and other blood factors in newborn infant, *J. Pediat.* 12: 785, 1938.
 45. (a) WASHBURN, A. H.: Blood cells in health young infants; the leukocyte picture during the first three months, *Am. J. Dis. Child.* 47: 993, 1934.
 - (b) WASHBURN, A. H.: Blood cells in healthy young infants; comparison of routine and special technics in differentiation of leukocytes, *Am J. Dis. Child.* 50: 395, 1935.
 - (c) WASHBURN, A. H.: Blood cells in healthy young infants; study of 608 differential leukocyte counts with final report on 908 total leukocyte counts, *Am. J. Dis. Child.* 50: 413, 1935.
 46. KATO, K.: Leucocytes in infancy and childhood . . . *J. Pediat.* 7: 7, 1935.
 47. LICHENSTEIN, A.: Hämatologiska studier å för tidigt födda barn under de första levnadsåren med särskild hänsyn till anämiska tillstånd, *Svenska läk.-sällsk. handl.* 43: 1533, 1917.
 48. HURTADO, A.: Studies at high altitude; blood observations on Indian natives of Peruvian Andes, *Am. J. Physiol.* 100: 487, 1932.
 49. TALBOTT, J. H.: Studies at high altitudes; morphology and oxygen combining capacity of blood, *Folia haemat.* 55: 23, 1936.
 50. DALTON, A. G., and SELYE, H.: Blood picture during alarm reaction, *Folia haemat.* 62: 397, 1939.
 51. BAAR, H., and STRANSKY, E.: *Klinische Hämatologie des Kindesalters.* Vienna, F. Deuticke, 1928.
 52. McLEAN, S., and CAFFEY, J. P., and others: Blood platelet counts in infants and in young children, *Am. J. Dis. Child.* 30: 810, 1925.
 53. LESLIE, E. I., and SANFORD, H. N.: Substances involved in coagulation of blood in new-born; prothrombin; quantitative and qualitative studies of platelets in normal infant, *Am. J. Dis. Child.* 51: 590, 1936.
 54. ARNETH, G.: Über das normale qualitative Thrombocytenblutbild des Säuglings, *Monatschr. f. Kinderh.* 73: 34, 1938.
 55. SANFORD, H. N.: Effect of gas anesthetics used in labor on the bleeding and coagulation time of the new-born, current researches, *Anesth. & Analg.* 5: 216, 1926.
 56. RODDA, F. C.: Studies with a new method for determining the coagulation time of the blood in the new-born, *Am. J. Dis. Child.* 19: 269, 1920.
 57. WADDELL, W. W., JR., and GUERRY, DuP., III: Effect of vitamin K on clotting time of

- prothrombin and blood, with special reference to unnatural bleeding of newly born, *J. A. M. A.* 112: 2259, 1939.
58. OWEN, C. A., HOFFMAN, G. R., ZIFFREN, S. E., and SMITH, H. P.: Blood coagulation during infancy, *Proc. Soc. Exper. Biol. & Med.* 41: 181, 1939.
 59. DAM, H.: Antihaemorrhagic vitamin of chick; occurrence and chemical nature, *Nature, London*, 135: 652, 1935.
 60. KATO, K., and PONCHER, H. G.: Prothrombin in blood of newborn mature and immature infants as determined by microprothrombin test, *J. A. M. A.* 114: 749, 1940.
 61. BRINKHOUS, K. M., SMITH, H. P., and WARNER, E. D.: Plasma prothrombin level in normal infancy and in hemorrhagic disease of newborn, *Am. J. M. Sc.* 193: 475, 1937.
 62. GROSSMAN, A. M.: Vitamin K for the pediatrician, with special reference to physiologic hypoprothrombinemia of newborn infants, *J. Pediat.* 16: 239, 1940.
 63. PONCHER, H. G.: Physiology of the blood in the newborn infant, *J. Pediat.* 20: 637, 1942. (In round table discussion on hemorrhage in the newborn infant.)
 64. (a) NORRIS, R. F., and RUSK, A.: Comparison of prothrombin levels of maternal and cord blood at delivery, *Surg., Gynec. & Obst.* 70: 1006, 1940.
(b) NORRIS, R. F., and BENNETT, M. C.: Plasma prothrombin values of mothers and infants at delivery; further studies, *Surg., Gynec. & Obst.* 72: 758, 1941.
 65. SALOMONSEN, L., and NYGAARD, K. K.: Prothrombin content in relation to early and late feedings of newborn . . . *Acta Paediat.* 27: 209, 1939.
 66. SANFORD, H. N., and SHMIGELSKY, I.: Is presence of bile and food in small intestine necessary for formation of prothrombin? . . . *Am. J. Dis. Child.* 63: 894, 1942.
 67. WADDELL, W. W., JR., and LAWSON, G. M.: Hemorrhagic diathesis of newborn . . . *J. A. M. A.* 115: 1416, 1940.
 68. NEVINNY, H.: Über die Blutstruktur bei Mutter und Kind, *Arch. f. Gynäk.* 144: 560, 1931.
 69. RUSH, A.: Comparison of fibrinogen and prothrombin levels of maternal and cord blood at delivery, *Surg., Gynec. & Obst.* 70: 922, 1940.
 70. RAPOPORT, M., RUBIN, M. I., and CHAFFEE, D.: Fractionation of serum and plasma proteins by salt precipitation in infants and children . . . *J. Clin. Investigation* 22: 487, 1943.
 71. CRANE, M. M., and SANFORD, H. N.: Substances involved in coagulation of blood of newborn infant; variations in fibrinogen content in normal infant, *Am. J. Dis. Child.* 51: 99, 1936.
 72. MCKHANN, C. F., COADY, H., DAVIES, J. A. V. D., and SMITH, C. A., Unpublished data.

Chapter VI

ICTERUS NEONATORUM

"THE SYMPTOM 'icterus' is not as frequent in any other period of life as it is in the first week and—a matter of particular importance—hardly ever as harmless." (Von Reuss¹).

"The degree of hyperbilirubinemia is a measure of the functional maturity of the infant at the time of birth." (Davidson, Merritt, Weech²).

In the first of these two quotations is expressed an incontestable fact; in the second, the conclusion of a well-supported theory. Taken together they form a sort of alpha and omega of a feature of neonatal physiology which has occasioned a great deal of investigation. It has also engendered a group of hypotheses so numerous, and frequently so erroneous, that it seems unwise to consider them in historical review. There is still less reason for such a presentation since so many excellent reviews are already available.¹⁻⁵

What percentage of newborn babies normally becomes jaundiced? Von Reuss has collected the observations of nine different authors whose statistics would place the incidence almost anywhere from 15 per cent to 100 per cent. These widely differing figures indicate a range of observational accuracy or inaccuracy which partially explains why so many different theories have been called forth to account for this symptom. To add to the confusion resulting from this subjectivity in the collection of data is the fact that several other types of icterus may occur in newly born infants as a result of definitely pathological states. The true frequency of physiologic icterus in completely normal infants depends upon such individual conceptions that exact data cannot be given, but probably at least 50 per cent and possibly as many as 75 per cent of babies may be expected to show some jaundice on some day or days shortly after birth.

The skin color at this period of life is notoriously changeable and, although dependent upon characteristic variations in capillary circulation, tends to an erythema which may easily mask a considerable pigmentation from the lighter yellow hue of bilirubin. Thus it is a common observation that pressure upon the infant's skin or mucosa with the finger, or better still, with a glass slide, can reveal a considerable state of icterus which disappears soon after removal of the pressure allows the blood to come flooding back into the superficial capillaries. Ada Hirsch⁶ pointed out not only that the

skin circulation could mask the presence of jaundice but that if soon after birth the circulation were naturally or mechanically impeded in certain areas, less yellow pigment would be brought by the blood and deposited there. Thus, in mild cases and before pigment has been widely distributed, the natural compression in the deep folds of the arms and legs renders those areas less brightly yellow than the more freely supplied parts, such as the face. She showed that icterus could be locally prevented by bandaging an arm or a leg in a bent position, and that the same sort of localized anemia could be brought about by applications of collodion anywhere upon the skin. On removal of the collodion, the skin was at first pale, then suffused with an excess of blood and somewhat edematous, and, finally, because of the resultant inrush of pigmented serum, became more yellow than the surrounding regions.

Hoffmann and Anselmino⁷ conducted somewhat similar observations by injecting histamine intradermally in newborn babies. In all but one of thirty normal infants, the resultant wheal became yellow in color after a few hours. The one infant whose local reaction was not pigmented never developed observable icterus, but neither did five of the others, although their histamine wheals seemed no less yellow than those of subsequently icteric babies. Obviously some skins must reveal icterus more easily than do others. Since the pigment pervades the body quite generally, the lachrymal and nasal secretions may be yellow, and, sometimes, the cerebro-spinal fluid also. The stools are practically always the same color as those of non-icteric infants, varying if at all towards a deeper yellow rather than towards any lessening of pigment. The urine is not abnormal in hue.

Just as it is impossible to state the number of normal infants who develop clinical icterus, it is also difficult to set any exact times at which the symptom may be expected to appear and disappear. Seldom or never is it observed at birth. In Davidson, Merritt, and Weech's carefully studied series,² 25 per cent of those infants showing jaundice did so during the first 24 hours, and in none did jaundice first appear after the sixth day of life. Since most normal infants stay in lying-in hospitals for not more than fourteen days, circumstances are not favorable for determining the maximum duration of observable jaundice. Von Reuss is probably correct in stating that it may last for a month, although the longer the condition lingers the more reason is there to suspect that it may actually be of pathological origin.

The term "physiological" jaundice, even though applied to an indubitably physiological process, may at times be somewhat mis-

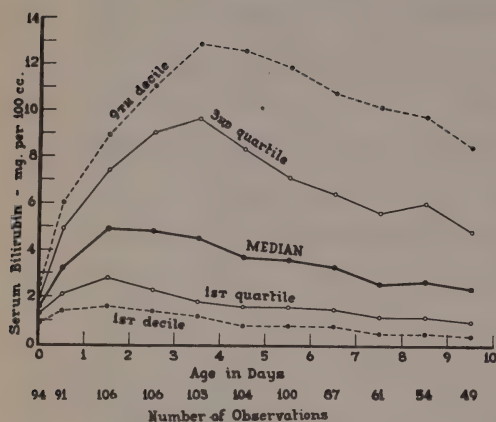


FIGURE 18

Distribution of bilirubin concentrations in the cord and later serum of normal infants during the neonatal period. (Davidson, Merritt, Weech, *Am. J. Dis. Child.*, 61: 958, 1941.)

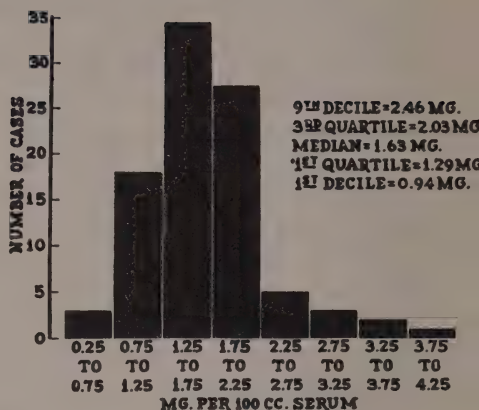


FIGURE 19

Concentration of bilirubin in umbilical cord serum of 96 normal infants. (Same source as Figure 18.)

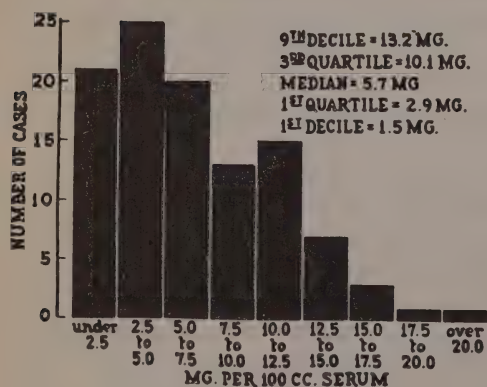


FIGURE 20

Maximum level of serum bilirubin attained during the neonatal period in 106 infants. (Same source as Figure 18.)

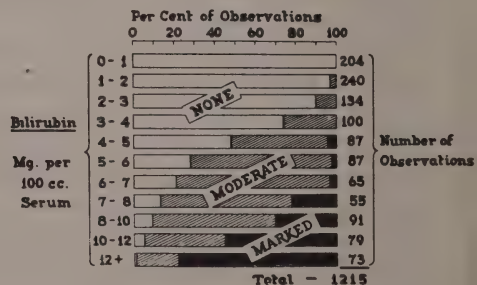


FIGURE 21

Relation between serum bilirubin concentration and degree of visible jaundice in 120 normal infants. (Same source as Figure 18.)

leading; a deep icterus of course means a flooding of the organism with bile pigment, a "cholemia" such as may not be borne without some alteration in life processes. Particularly in smaller infants, one may occasionally see temperature instability, sluggishness, poor appetite, or vomiting, with no other demonstrable cause than a marked jaundice. Thus, as with dentition, although physiological in etiology, icterus neonatorum may be mildly pathological in effect.

Icterus neonatorum is produced by an excess of bilirubin. This pigment exists in varying but almost always excessive quantities in the blood of all infants at birth, and its amount increases during the following two to four days to reach a peak which may be more than ten times the level in the umbilical cord serum. This phenomenon is indisputable, and rests upon determinations either of bilirubin itself or of the icteric index, as recorded especially by Yllpö,³ Davidson and his associates, Hirsch,⁶ Bonar,⁸ and by other workers.^{5,9-12} The facts appear most graphically in charts from the data of Davidson, Merritt, and Weech² which have been reproduced here with their kind permission. For the evaluation of this data attention should be called to the fact that in the normal blood serum of adults, bilirubin may be present to the amount of 0.1 to 0.5 mgm. per 100 cc. Supposedly the icteric index in normal blood is below five units, whereas that of cord blood was found by Bonar⁸ to average 12 units, the figure rising to an average of 53 units on the fifth day in a group which included both icteric and non-icteric subjects.

The facts seem sufficiently clear-cut when presented thus, but the tendency to expect exact correlations between the degree of increase in the blood bilirubin on the one hand and the presence or absence of observable jaundice on the other has led to controversy and doubts in the field of interpretation.^{13,14} Thus in certain infants, blood bilirubin or icteric index levels can be obtained which should predictably have called forth clinical jaundice, but sometimes such individual infants have not become yellow whereas other infants with somewhat smaller quantities of blood bilirubin or lower icteric indices have done so. A most satisfactory elucidation of this matter was graphically presented in the diagram (Fig. 21) in which Davidson, Merritt, and Weech correlated their biochemical and clinical data. There is obviously a strong and significant tendency for the more bilirubinemic infants to develop the most pronounced icterus, although it will be noted that exceptions of both sorts occurred in their series; some infants whose blood contained much pigment did not become visibly jaundiced, and some became jaundiced in the

absence of a high level of blood bilirubin, so that as those authors were careful to point out, "a critical level of serum bilirubin, above which icterus is present and below which it is absent, does not exist." There can be no reason for this except a variation in the superficial circulation and structures, by virtue of which jaundice is more easily revealed by certain infants than by others.

Elevated at birth, rising to a peak during the next few days, and roughly correlated with the degree of visible icterus, the blood bilirubin begins to decrease usually by the fifth day. Davidson, Merritt, and Weech have called attention to the fact that the higher the level in the cord blood itself, the higher will usually be the peak of the rise, and the later will the decline begin. Bonar's data on the icteric index show the same facts. Explanation of these points requires explanation of the source and fate of the pigment.

When Van den Bergh described a method for differentiating bilirubin, as to whether or not it had been excreted by the liver cells, numerous investigators^{6,14,15} were quick to subject the pigment in the blood of the newborn to this test. The result was always the same. The excessive bilirubin consistently gave the indirect Van den Bergh reaction and had therefore not passed through the liver cells. Thus it became possible to abandon all theories based upon any sort of obstruction to the outflow of bile from the liver. But it became necessary to explain why, although the fetus is not yellow *in utero* it is born with a bilirubinemia which, through no outstanding fault of the liver, increases to a varying degree but always subsides to reach the insignificant amount normal for the older organism. It was further necessary to include in such an explanation a satisfactory reason for the fact that premature and immature infants have been universally noted to display an even more obvious and prolonged saturation with bilirubin than that of full term infants. If the explanation could be correlated with data obtained by measuring the amount of bile pigment in the meconium of the fetus and in the intestinal contents of the newborn infant, so much the better and the more complete. And, finally, if it could be explained why newborn animals (with occasional and dubious exceptions) regularly fail to show either an increase of blood bilirubin or the presence of icterus,^{3,4,16} all parts of the problem would be solved.

It has been shown in an earlier chapter that the hemoglobin concentration and number of red cells are both on the increase during human fetal life and reach a peak at or soon after birth. It is probable that these increases are, at least in part, a reaction to the relative anoxia of the intra-uterine state. When oxygen becomes

more easily available by pulmonary respiration after birth, the call for hemoglobin is a less urgent one, and a compensatory destruction of erythrocytes and liberation of hemoglobin for excretion follows. Goldbloom and Gottlieb¹⁷ have shown that the blood will respond in just this fashion if normal experimental animals are kept for a period of weeks at a low oxygen tension and then returned to the conditions of ordinary atmosphere. These workers studied guinea pigs which were acclimatized to oxygen conditions such as might be found at an altitude of 18,000 feet. Their return to normal air was followed by a decrease in the resultant polycythemia and by the appearance of a positive indirect Van den Bergh reaction (1 to 2 units) together with an increase in the icteric index of the blood. The same reduction of an acquired polycythemia is a well-known adjustment in the blood of human subjects after a sojourn at high altitudes, and all the manifestations mentioned are directly comparable to those of the infant upon release from the conditions of fetal life.* An explanation is thus afforded for the general background of bilirubin excess which shows itself externally in icterus. Bile pigment is flooding the body at a faster rate than it can be removed.

The abnormal amount of bilirubin in the infant's blood at the moment of birth demands a further explanation, since at that early period no postnatal destruction of red blood cells has been called forth. To defer for the present the question of the origin of this substance in the fetus, it must be mentioned that infants having particularly high levels of serum bilirubin in the umbilical cord blood have a definitely greater tendency to develop higher degrees of bilirubinemia thereafter than do infants with relatively low levels of serum bilirubin at birth.^{2,3,6} Moreover, in infants of the former group, hyperbilirubinemia tends to be more prolonged in duration than in those of the latter. This cannot mean that in such infants by some process of foreordination excessive blood destruction sets in before birth and continues at a more than average degree through neonatal life. It can scarcely be accounted for except by some inadequacy of the liver in performing its function of taking bilirubin from the blood and excreting it into the bowel, a shortcoming which, although it may be relatively slight, would be all the more evident when the large excretory burden of postnatal hemolysis falls upon that organ.

Yllpö³ found that the amount of bilirubin in the meconium at

* See Chapter V for discussion of hemolysis and erythrocyte fragility in newborn infants.

birth bears a generally inverse relationship to the development of manifest jaundice a few days later, and observations of the same sort were made by Schwartz¹⁸ and by Nakamura.¹⁹ This would suggest that the livers of those infants in whom jaundice developed might be limited in ability to excrete bilirubin. Lepehne's measurements of bilirubin in the bowel contents¹⁵ did not show a correlation with the presence or degree of icterus, but it is important to note that the samples studied were not obtained until the second post-natal day, or even somewhat later, when great variations existed in the amount and the course of the bilirubinemia. Volhard⁴ has argued from Yllpö's figures that a good correlation exists between the out-pouring of bilirubin by the liver into the intestine during the first five days of life and the escape of the infant from developing manifest jaundice.

Hepatic inadequacy in this regard did not, however, reveal itself in Lin and Eastman's direct measurements of the excretory capacity of the liver²⁰ when calculated amounts of bilirubin were injected into the umbilical circulation at birth. The crux of these experiments was the speed with which the artificially introduced excess of pigment was cleared from the blood, as measured by its concentration in capillary specimens thereafter. Compared with results of the same tests performed upon adult subjects, the livers of these newborns seemed to function normally, nor was any difference noted to distinguish certain infants who later developed icterus neonatorum from the other members of the group. Lin and Eastman could not see from these data how functional immaturity of the liver could play any part in the development of physiologic jaundice. A possible reservation as to this conclusion might be based upon the dosage of the test substance used. Since the blood volume at birth is in the neighborhood of 10 per cent of body weight, the use of 3 mgm. of bilirubin per kilogram must have added (to that already present) about 6 mgm. of bilirubin per 100 cc. of serum, an amount much in excess of the 90 percentile level found in cord blood by Davidson and his colleagues.² In other words, it is possible that so much bilirubin was being presented for hepatic excretion that relative degrees of liver immaturity were concealed by the experiment. It is known that bilirubin excretion tests are generally unreliable in jaundiced patients.

The excess bile pigment in the umbilical vessels at birth could obviously not originate by postnatal hemolysis, nor could it have crossed the placenta from a maternal oversupply, as the blood of the pregnant woman at term and during delivery is normal in bile

pigment content and thus usually contains definitely less bilirubin than does the cord blood. Nor is it probable that the status of fetal blood, the hemoglobin and erythrocytes of which are still being augmented, would of itself be compatible with any excess of a material formed there by hemolysis. Schick²¹ has offered the explanation that the bilirubin in the infant's serum at birth is a consequence of maternal blood destruction which he believed might take place locally in the placenta, there providing the fetus with a depot from which to absorb hemoglobin or, at least, iron, and incidentally bilirubin. That a process of this sort might be related to the excessive bilirubinemia of premature infants is borne out by Wagner's measurements of the iron content of premature and full-term placentas.²² The data showed a much greater placental iron content at premature birth. It thus seems believable that the fetus may obtain a significant quantity of the breakdown products of blood from placental depots, and that opportunities for this absorption are somewhat greater a month or so before term than at full gestation. Schick and his colleagues²³ have recently shown the icteric index of umbilical cord blood to be somewhat higher at premature than at full-term delivery. The differences, though of slight statistical significance, were in keeping with the belief that the premature subject may receive a particularly large amount of bile pigment from the placenta, and that hepatic function may not deal with this excess so adequately as is the case when greater maturity is attained. The level of bilirubin in the fetal blood is presumably little above the excretory capacity of the liver. After birth a still larger amount of bilirubin is presented for hepatic excretion by virtue of postnatal hemolysis of the infant's own blood cells; the relative ability of the liver to meet this demand is already recognizable and predictable from its prenatal performance, as shown by the state of serum bilirubin in the cord blood.

If the livers of all newborn infants could always be counted upon for a like excretory ability and if the degree of icterus neonatorum were thus solely dependent upon the amount of postnatal readjustment made by the infant's blood cells, the amount of jaundice or hyperbilirubinemia should show an impressive correlation with the degree of neonatal change in erythrocyte counts and in hemoglobin. Several authors^{8,11,12,24-26} have sought for data on this point, and their results have either shown a slight and statistically insignificant agreement between amount of blood destruction and amount of jaundice, or a rather disappointing lack of correlation. Yet, when the various postnatal adjustments of body fluids are taken into

consideration, it is not surprising that the results have been as stated, although they do suggest variability in liver function. A more fruitful field of observation has been the possible effect of the relative polycythemia produced by late clamping of the cord at birth. It was early appreciated²⁷ and has lately been abundantly proven²⁸ that the possession of an extra quantity of blood obtained while the cord pulsates after birth leads with significant frequency to icterus neonatorum a few days later. Book²⁸ showed that measurable icterus occurred in 73 per cent of such infants but in only 32 per cent of those whose cords were clamped early.

Data which are of interest, though somewhat difficult to interpret exactly, were secured by Scherbak,¹⁶ who analyzed the frequency with which non-identical and identical twins developed icterus. His findings showed:

	Non-identical	Identical
Number of twin births	165	45
Both twins icteric	76 (46%)	21 (47%)
Neither twin icteric	64 (37%)	23 (51%)
One icteric, one non-icteric	25 (17%)	1 (2%)

Since identical twins behave alike as regards the development of jaundice it would seem that the factors which produce icterus of the newborn are associated with deeply ingrained physiological attributes of the infant. This would apply to the maturity or immaturity of the liver and would declare itself exactly as revealed in the data above.

Knowledge as to the stool and urine content of urobilin during the newborn period has been furnished by Reuss²⁹ and recently by Ross, Waugh, and Malloy.¹¹ Again the findings argue for some degree of hepatic inadequacy in babies who develop icterus neonatorum. Ross and his associates found that although large amounts of urobilin (as well as of bilirubin and biliverdin) were present in the stools during the first week of life, the average total excretion was somewhat less in the icteric than in the non-icteric infants. This difference, as they point out, is contrary to what one would expect in a purely hemolytic type of jaundice. In the same groups of patients, the average total urobilin excretion in the urine was lower in the infants with jaundice than in those without. Since in the presence of a normally functioning liver increased blood destruction is accompanied by an increased urobilinuria³⁰ the findings in these infants suggest a failure of normal hepatic action.

Why should newborn animals fail to become jaundiced? Not

merely because of skin color and peculiarities of capillary circulation, since Yllpö³ is authority for the fact that in dogs, goats and—almost always—in horses, no excess or increase in bile pigment can be found in the blood serum after birth. It is true that in many animals³¹ the number of erythrocytes continues to rise in the days or weeks after birth, but it is equally true that the total hemoglobin per unit of blood undergoes a rapid fall, so that the mean corpuscular hemoglobin is sharply decreased. It is difficult to see, for example, why newborn rats,³² whose hemoglobin content diminishes from 10.31 gm./100 cc. at birth to 7.54 gm. at 20 days (even though the erythrocyte count nearly doubles during the same interval) escape a hyperbilirubinemia. However, growth in body, which means in blood volume also, might be sufficiently rapid to explain the hemoglobin deficit per unit of blood, and the liver of the young animal may be a more efficient organ than that of the human infant. An investigation of the quantity of bile in the intestinal contents of neonatal animals would settle this interesting although perhaps academic problem.

Recapitulation of our present knowledge of icterus neonatorum might be expressed in terms resurrected from earlier controversies on the subject. Is it a "hematogenous" or "hepatogenous" jaundice? It would seem to have elements of both, although to be an essentially hematogenous process. The hematogenous element is modified by the hepatogenous one to a degree varying with the maturity of the infant at birth.

CLINICAL SUMMARY

Since it results in part from hepatic immaturity, the physiological jaundice of newborn infants is usually more severe and may be more prolonged among those prematurely born. While the icterus may proclaim itself in perhaps 50% of all infants, and usually begins between the first to the fifth day, the underlying excess in blood bilirubin is present at birth in every infant and rises to a peak on the second to fourth day. This hyperbilirubinemia is in large degree due to post-natal hemolysis. Inadequacy of liver function contributes to its presence and persistence. In the more jaundiced babies there may be mild symptoms such as temperature instability, lassitude, and anorexia. The fact that physiological jaundice is not visibly distinguishable from definitely pathological types of jaundice prone to occur in the same period is perhaps worthy of mention, though a discussion of these types is outside the scope of this chapter.

BIBLIOGRAPHY

1. VON REUSS, AUGUST: The Diseases of the Newborn, London, J. Bale, Sons and Danielsson, 1920.
2. DAVIDSON, L. T., MERRITT, K. K., and WEECH, A. A.: Hyperbilirubinemia in newborn, Am. J. Dis. Child. 61: 958, 1941.
3. YLPÖ, A.: Icterus neonatorum und Gallenfarbstoff-sekretion beim Foetus und Neugeborenen, Ztschr. f. Kinderh. 9: 208, 1913.
4. VOLHARD, E.: Ueber die hämatogene Hyperbilirubinämie und den hämatohepatogenen Ikterus der Neugeborenen, Ergebn. d. inn. Med. u. Kinderh. 37: 465, 1930.
5. GOLDBLOOM, A., and GOTTLIEB, R.: Icterus neonatorum, Am. J. Dis. Child. 38: 57, 1929.
6. HIRSCH, ADA: Die physiologische Ikterusbereitschaft des Neugeborenen, Ztschr. f. Kinderh. 9: 196, 1913.
7. HOFFMANN, F., and ELSELMINÖ, K. J.: Über die Bedeutung der Durchlässigkeit der Haut-capillaren für das Zustandekommen des Icterus neonatorum, Arch. f. Gynäk. 143: 500, 1931.
8. BONAR, B. E.: Icterus index in new-born infant, Am. J. Dis. Child. 50: 1143, 1935.
9. WEINER, S. B., and REINER, M.: Icteric index in newborn, Proc. Soc. Exper. Biol. & Med. 41: 83, 1939.
10. SNELLING, C. E.: Icterus neonatorum, J. Pediat. 2: 399, 1933.
11. ROSS, S. G., WAUGH, T. R., and MALLOY, H. T.: Metabolism and excretion of bile pigment in icterus neonatorum, J. Pediat. 11: 397, 1937.
12. WAUGH, T. R., MERCHANT, F. T., and MAUGHAN, G. B.: Blood studies on newborn; direct and total blood bilirubin; determinations over 9-day period, with special reference to icterus neonatorum, Am. J. M. Sc. 199: 9, 1940.
13. HELLMUTH, K.: Untersuchungen über Bilirubinämie beim Neugeborenen, zugleich ein Beitrag zur Genese des Icterus neonatorum, Monatschr. f. Geburtsh. u. Gynäk. 54: 341, 1921.
14. SCHIFF, E., and FAERBER, E.: Beitrag zur Lehre des Icterus neonatorum, Jahrb. f. Kinderh. 47: 245, 1922.
15. LEPEHNE, G.: Zur Kenntnis des Icterus neonatorum, Monatschr. f. Geburtsh. u. Gynäk. 60: 277, 1922.
16. SCHERBAK, A. L.: Ist die Gelbsucht der Neugeborenen vermeidbar? Zugleich ein Beitrag zur Zwillingsstatistik, Zentralbl. f. Gynäk. 60: 1934, 1936.
17. GOLDBLOOM, A., and GOTTLIEB, R.: Studies on icterus neonatorum; production of icterus in animals following prolonged anoxaemia, J. Clin. Investigation 8: 375, 1930.
18. SCHWARTZ, P.: Zur Frage des Icterus neonatorum, Ztschr. f. klin. Med. 100: 117, 1924.
19. NAKAMURA, H.: Mitt. Jap. Gesellschaft. f. Gynäk. 31: 94, 1936. Quoted by Reuss, A., Monats. f. Kinderh. 72: 409, 1938.
20. LIN, H., and EASTMAN, N. J.: Behavior of intravenously injected bilirubin in newborn infants, Am. J. Obst. & Gyneec. 33: 317, 1937.
21. SCHICK, B.: Der Icterus neonatorum, eine Folge des Abbaues mütterlichen Blutes, Ztschr. f. Kinderh. 27: 231, 1920.
22. WAGNER, R.: Icterus neonatorum und Eisengehalt der Placenta, Ztschr. f. Kinderh. 27: 251, 1920.

23. SCHICK, B., WEINER, S. B., and REINER, M.: Icterus index of cord blood; genesis of icterus neonatorum, *Am. J. Dis. Child.* 64: 655, 1942.
24. HEIMANN, FRITZ: Zur Lehre des Icterus neonatorum (Systemische Blutuntersuchungen) *Ztschr. f. Geburtsh. u. Gynäk.* 69: 164, 1911.
25. MARTIN, L. C., and EVANS, S. M.: Blood counts of newborn infants in relation to icterus neonatorum, *Arch. Dis. Childhood* 10: 355, 1935.
26. MITCHELL, J. M.: Relationship of jaundice to weight and blood values in the newborn infant, *Am. J. Dis. Child.* 38: 518, 1929.
27. VIOLET, G.: Ueber die Gelbsucht der Neugeborenen und die Zeit der Abnabelung, *Arch. f. path. Anat.* 80: 353, 1880.
28. BOOK, N.: Icterus neonatorum, *Canad. M. A. J.* 33: 269, 1935.
29. VON REUSS, A. R., quoted by Hirsch, ref. 6 above.
30. ELMAN, R., and McMASTER, P. D.: Relation between urobilin and conditions involving increased red cell destruction, *J. Exper. Med.* 42: 619, 1925.
31. WINDLE, W. F.: *Physiology of the Fetus: Origin and Extent of Function in Prenatal Life.* Philadelphia, W. B. Saunders, 1940.
32. BRUNER, H. D., VAN DE ERVE, J., and CARLSON, A. J.: Blood picture of rats from birth to 24 days of age, *Am. J. Physiol.* 124: 620, 1938.

Chapter VII

METABOLISM AND HEAT REGULATION

Section 1 . . . Energy Metabolism

Section 2 . . . Body Temperature

Section 3 . . . Clinical Summary

ENERGY METABOLISM

IN THE GENERAL field of energy metabolism in the newborn, the subjects which have attracted interest are, first, the level of fetal heat production and its relationship to neonatal heat production; second, the basal heat production shortly after birth as compared with that in older childhood and adult life; third, the evidence obtainable from studies of the respiratory quotient as to the food substances used in the days of transition between abandonment of placental nutrition and assumption of nutrition by the alimentary tract; and fourth, the amount of added energy needed beyond the basal requirement in the early days of life for activity and growth. In most of these regards special attention must be devoted to the premature infant as presenting a unique situation.

The first question listed above, the comparison of fetal and neonatal metabolism, requires some accurate means of measuring heat production in the fetus, and for this it has been understandably impossible to adapt the mechanisms of direct calorimetry. An indirect application of this technique has been utilized by Bohr,¹ who determined the carbon dioxide production of gravid animals whose abdominal and uterine walls had been opened so that a ligature could be intermittently tightened and loosened around an umbilical cord. The observation of a consistent and measurable lowering of CO₂ production during periods when a fetus was thus cut off from the mother allowed calculation of fetal metabolic activity, which in these studies appeared to be about as great in relation to a unit of fetal weight as was that of the mother per unit of maternal weight.

A variation of this technique which considers maternal and fetal metabolism together has been utilized by observers^{2,3} who have taken repeated measurements of the heat production in experimental animals (or in women) during pregnancy and soon after delivery. Observations of this sort have apparently led to striking results, as when the metabolism measured for the infant alone after

birth has proved to be almost exactly equal to the difference in the maternal metabolism before and after delivery. But these data are difficult to interpret with regard to such complications as are offered by the variation in maternal heat production to be expected during pregnancy, and the metabolic effects of placenta, membranes, and amniotic fluid. An excellent analysis of the subject is presented by Needham in his second volume on *Chemical Embryology*.⁴ The general impression left by the authors of such observations is that the rate of heat production per unit (by weight) of human fetal tissue does not increase or decrease very much during intra-uterine development and is as much as, or perhaps somewhat greater than, that of an equal amount of maternal tissue. This conclusion was accepted by Hasselbalch⁵ in 1904, but has lately been challenged.

Work in which direct measurements of gas levels in samples of cord blood have been made has given a different conception of the fetal metabolic state. Cohnstein and Zuntz,⁶ published figures obtained in this way which showed the sheep fetus *in utero* to use as little as 1.16 cc. of oxygen per kilogram of its weight per minute, as compared with a figure (from another author) of 5.8 cc. for the adult sheep. Since the passage of blood through the fetus does not follow a circuit such as that from the left ventricle to the right auricle in the adult, because at least some crossing and admixture of currents takes place in and near the fetal heart, Barcroft⁷ has attempted a calculation to correct for these factors. Applying this to measurements of oxygen in the umbilical vessels of the fetal sheep he found that organism to consume about 2.5 cc. of oxygen per kilogram per minute. In a later series of measurements Barcroft, Kennedy and Mason⁸ arrived at perhaps more accurate figures which average 4.3 cc. of oxygen used per kilogram per minute. For comparison, Barcroft cites the figure given above of 5.8 cc. for the adult sheep and also one from another source of 28 cc. per kilogram per minute. In either case the fetus would seem, throughout gestation, to be using less oxygen and therefore to be producing considerably less heat (per unit of body mass) than do extra-uterine animals.

On a somewhat less secure foundation of essential data, Haselhorst and Stromberger⁹ have attempted to make similar calculations for the human fetus before birth. They concluded that oxygen is utilized and, therefore, that fetal heat production takes place, to the degrees indicated in the following table.

The figure for the neonatal period seems high in comparison with that for the fetus but is interestingly near an average of 6.6 cc.

O₂ per kilogram per minute, which can be roughly computed from Benedict and Talbot's¹³ data from human infants on the first day. In any case the human organism *in utero* appears to have a low degree of metabolic activity. And this is certainly in keeping with what might be expected in view of the fetal state of comparative inactivity of organ functions, depressed muscle tone, and, in particular, insulation from heat loss.

As to the second question, the metabolism of the infant shortly after birth, a number of studies have been made of the heat production at this time. Here the small size of the subjects and certain

TABLE 20
OXYGEN CONSUMPTION (AS AN INDEX OF METABOLISM) DURING HUMAN
DEVELOPMENT

	02 per Kilogram per Minute
Human fetus before labor	1.25 cc.
Human infant before breathing	1.50 cc.
Human infant during first week	6.4-7.9 cc. (Schadow ¹⁰)
Premature infant during first day	6.3-6.4 cc. (Schlossman, Murchhauser ¹¹)
Human adult	3.9 cc. ¹²

other considerations have made very exacting measurements necessary. Even with their application, the results tend to be spread over a sufficiently wide range so that one can understand the reasons for such statements as that in a standard textbook of pediatrics,¹⁴ that "the basal metabolism in early infancy is not accurately known." However, it would probably be more correct to say that all young infants do not seem to have metabolic rates confined between narrow and rigid limitations so that no exact figure can be applied to all newborns. The standard researches on the subject, those of Benedict and Talbot, were carefully designed to circumvent all sources of error. Their two monographs,^{13,15} forming a major portion of the source material, present critical surveys of the more important preceding literature. Aspects of the problem especially explored in these surveys and in the authors' own data, have been the relation of heat production in young infants to bodily activity and pulse rate, the proper standard of reference in terms of which neonatal heat production ought to be expressed, and the character of nutrition available to the infant in the first few days, as shown by the type of respiratory quotient.

Measurements of heat production in extra-uterine organisms are usually given in terms of calories produced per unit of time, and

for any individual this figure will vary in general accordance with body size, activity, and other considerations. If activity is reduced to a minimum and other factors, such as the digestion of food, are eliminated, the heat production observed will be the basal heat production or basal metabolism. If all disturbing factors except those of digestion be removed, heat production, though not basal, may be called minimal. Since infants are not "normal" when food is withheld so long as to eliminate the digestion factor from their metabolic activity, many measurements made during the neonatal period are, strictly speaking, not basal but minimal. In either case the results still bear a relationship to the size of the organism producing the heat.

In one of 94 infants during the first day of life, Benedict and Talbot¹³ observed minimal heat production of 95 calories per 24 hours; in another the value was 193 calories. The latter was the largest infant in the group, while the former, although small, was not the smallest. An average of results in these 94 infants gave a minimal heat production of 42 calories per kilogram of weight per 24 hours, or 1.75 calories per kilogram per hour. Benedict and Talbot were careful to direct attention to the wide scattering in their results, and were not very happy about setting up 1.75 calories per kilogram per hour as any sort of exact "normal" standard of basal heat production in the newborn infant. Nevertheless, it is a figure which, when compared with the general adult one of about one calorie per kilogram per hour,¹⁶ indicates that *weight for weight*, the infant at birth is somewhat more active metabolically than is the adult, although less so than is the child of one to three years, whose basal heat production is well over two calories per kilogram.¹⁷

In 1883 Rubner first drew attention to the importance of surface area in regulating heat loss from the body to its surroundings. He put forward a principle since known as Rubner's Law, or the Law of Rubner and Richet, that the heat production of all warm-blooded creatures is approximately the same if expressed in terms of their surface area. The "Law," while coming fairly near the truth is not actually true, and it is in this very matter of infant and adult metabolic processes that its partial value as well as its inaccuracy as an exact statement of fact, becomes evident. Discussion of the various formulae for computing the surface area of the body may be found in DuBois' or in Feldman's books,^{16,18} the effect of the general principle involved may be illustrated in a table excerpted from the latter source.*

* Some aspects of this subject in relation to respiration in infancy have been considered in Chapter III.

It will be noted that small human beings have greater surface areas as compared with their weights. The same is true of any solid body. The newborn infant has 15 per cent as much surface area as has the adult, but its weight is only about 5 per cent that of the adult. Or, for each kilogram of weight, the infant has about 700 square centimeters of surface, while the adult has about 200, or less than one-third as much surface per kilogram. Rubner and his followers expected the basal metabolism of the infant and the adult to be reconciled to the same order of magnitude if expressed according to surface area (as is the case with small and large animals), and

TABLE 21
BODY WEIGHTS AND SURFACES AT VARIOUS AGES

Age	Body Weight (gm.)	Per cent of Adult's Weight	Surface Area (sq. cm.)	Per cent of Adult's Surface	Area of Surface per Kilogram Wt. (sq. cm.)
4 days, pre-mature	1,505	2.4%	1,266	9.0%	841
15 days	2,980	4.8%	2,129	15%	711
6 months	5,138	8%	2,961	21%	576
1 year	9,095	14.5%	4,800	34%	527
6 years	16,065	25%	7,330	52.5%	456
12 years	21,782	34%	8,961	63%	412
43 years	63,650	100%	14,079	100%	221

indeed it has been shown in general and will be seen from the next paragraph that the metabolism per unit of surface is somewhat more nearly uniform than that per unit of weight, when infants and adults are compared. But it is *not* the same, and therefore no "Law" of physiology is involved, since the facts do not allow a law to be formulated. The facts of metabolic studies in general do suggest that surface area is a more valid standard for metabolic prediction than is body weight.

To Benedict and Talbot can be given much of the credit for insisting that the heat production shortly after birth is definitely lower per surface unit than it is in adult life. They¹³ found an average of 25.5 calories to be produced per square meter of surface per hour during periods of minimal activity in the first week of life. By the same standards Murlin and his colleagues¹⁹ determined the heat production of such infants to be just over 29 calories. That the level which could be called normal is still not a very narrow one was shown by a range for supposedly equally "normal" babies of figures

from 19.1 to 30.5 calories per square meter in Benedict and Talbot's observations. However, even when the highest of these is compared with the normal basal heat production at two years of age of about 48 calories per square meter per hour,¹⁵ and the usually accepted value for adults of 35 to 40 calories,¹⁶ it is clear that the basal heat production shortly after birth is actually depressed as compared to what it becomes in later life, if the comparison is made on the most logical basis.

The discussion above is only with regard to the minimum heat production of resting subjects. When the infants studied¹³ indulged in muscular activity, such as forceful crying, heat production rose usually by about 65 per cent above the minimum and, in some instances, to more than 200 per cent. Murlin, Conklin, and Marsh¹⁹ found somewhat different values for active infants during the first two weeks of age, which they expressed by saying that "crying one per cent of the time raises the metabolism by one per cent," so that they conceive heat production to be increased 100 per cent by such activity. The subject is of more than academic interest since it not only indicates a reason for variations in metabolic data secured from infants but it also demonstrates that a certain caloric intake may be nutritionally inadequate for a restless infant, although satisfactory for a somnolent one of the same size.

Besides calling attention to the wide scattering of minimal heat production measurements from newborn subjects, Benedict and Talbot¹³ also observed that none of the existing formulae for predicting the metabolic performance could be applied with much accuracy at this time of life. Searching for a more adequate formula they devised one which took into account length and surface in the expression:

$$\text{Total calories} = \text{length in cm.} \times 12.65 \times 10.3 \sqrt[3]{\text{Wt.}^2}$$

The last factor ($10.3 \sqrt[3]{\text{Wt.}^2}$) is Lissauer's formula for computing body surface. The application of the longer formula to the length and weight of normal infants during the first week of life resulted in a prediction of calories of heat produced during 24 hours which was found to be very near the actual amount measured by numerous metabolism chamber observations. The results in 48 infants tended to be usually well within 7 per cent (plus or minus) of the prediction. Levine and Marples²⁰ have devised a nomogram for predicting the expected basal metabolism of normal infants in general, basing their calculations upon infants most of whom were beyond the neonatal age period. The nomogram, although it extends to weights and lengths as low as 2 kilograms and 45 centimeters, tends to give

values which are not so near the actual caloric output in the first week as are the figures obtained by using the $\text{length} \times 12.65 \times 10.3 \sqrt[3]{\text{Wt.}^2}$ formula; it is very satisfactory for slightly older subjects, from whose data it was, of course, largely constructed.

If the basal metabolism is low at birth, and, according to Table 20, probably even lower during fetal life, the premature infant might be expected to show evidences of scanty heat production shortly after birth. This has proven to be the case. From what has been said, it is evident that a premature infant about half as heavy as a "mature" one will have somewhat more than half as much surface area. The premature infant's heat production, although it may be a little greater than that of the full term infant if considered with regard to its weight, will nevertheless be low if referred to its extensive surface, and any comparisons between premature and other infants must, of course, be made with this in mind. Thus, if a premature infant has lower heat production per unit of surface than a full term infant, his metabolic performance is certainly the lower of the two.

Hasselbalch, in 1904,⁵ gave figures for CO_2 production which indicated that at less than two hours of age the heat production of a few prematures was lower indeed even when referred to weight, than that of equally young "mature" infants. Premature infants of somewhat greater age were shown by Talbot, Sisson, and their colleagues²¹ to be living at what they called "strikingly low" rates of metabolism. Presentation of their material in chart form makes reduction of it to an arithmetical tabulation difficult and perhaps unwise in view of the hazards of comparison with larger subjects, but the authors stated that no matter how they were charted the results were less than those of full-term subjects. "The low metabolism," they wrote, "seems to be dependent upon the fact that there is a very small amount of active heat-forming tissues in these incompletely developed infants."

Later the same authors extended their observations to a larger number of infants;²² from their augmented data the same conclusion appeared. Eight of the twenty-one premature subjects they studied, for example, produced less than 41 calories per kilogram per hour, a figure in their experience below the average of normal metabolism after full term birth. In the smaller prematures the metabolism per unit of weight was lower than in the larger members of the group—a circumstance which appeared to be definitely related to the chronological age as well as to the size. The same tendency for the results to be lower in the smaller and younger in-

infants appeared when they were expressed in terms of body surface. The heat production per square meter of surface in smaller pre-matures was below that of normal infants, while in those subjects weighing more than 2.1 kilograms the heat production per surface unit was slightly above that to be expected in the newborn "ma-ture" child. One may thus expect to encounter either slightly higher or slightly lower metabolism after premature than after full gesta-tion, but the more premature a baby, the more confidently it may be expected to have a poor heat production, a fact from which the authors predicted that "if a premature infant were exposed to cold there would presumably result a rapid loss of heat from the body, but not a compensatory increase in heat formation, because it is incapable of forming more heat in early life. As a consequence . . . the body temperature becomes subnormal. If this condition is al-lowed to continue over any length of time, death nearly always results." To some extent, the validity of the last sentence may be challenged (see p. 160). The authors also learned that the prema-ture infant produces less heat on his expected birth day than does the full term infant during any day of his first week of life, and that activity, when manifested in a premature subject, increases the heat production above the basal level by an average of 40 per cent more calories. This may be compared with 65 per cent as the aver-age increase for activity in Benedict and Talbot's series of normal newborns, and 100 per cent in Murlin's observations. It indicates very clearly the disadvantage of the premature in the field of heat production.

Marsh and Murlin²³ investigated somewhat larger (although rather younger) premature infants, and found their heat output also to be low if compared with other organisms on the basis of body surface. Their figures are:

TABLE 22
METABOLISM OF NEWBORN INFANTS (MARSH AND MURLIN) COMPARED
WITH ADULT NORMALS

	Average Calories		
	Total Basal (per hour)	(per sq. m./hr.)	(per kg./hr.)
Premature Infants	6.48	26.25	2.04
Full term Infants	6.67	29.16	2.00
Adult Averages ¹⁶		35-40	1.00

Since these infants were somewhat larger than those prematures mentioned above whose metabolism was raised about 40 per cent by muscular activity, it is understandable that, as the authors report, these achieved metabolic increases nearer to 100 per cent when they cried and kicked.

Gordon and Levine's data from a large group of observations²⁴ were presented in a chart which also includes measurements from a number of full term infants. This is reproduced here not only because it indicates the general principle that the smaller prematures

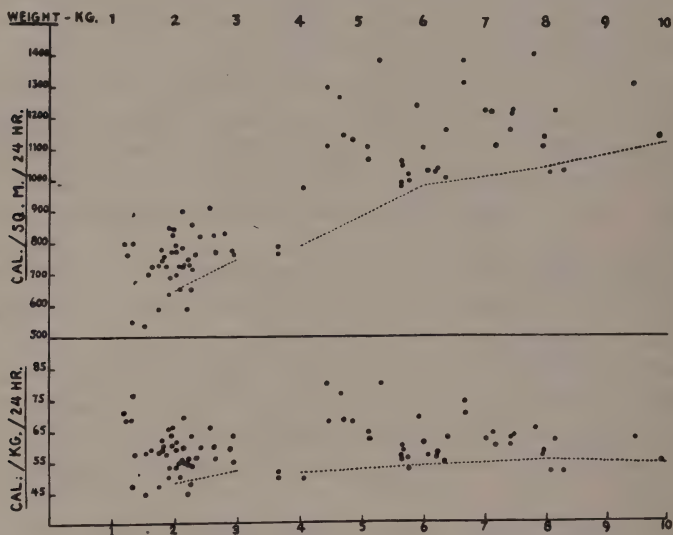


FIGURE 22

Two sets of data indicating the relationship of increasing weight to basal metabolism. Dots indicate single determinations by Gordon and Levine.²⁴ Broken line shows curve derived from data of Benedict and Talbot¹³ for full-term infants, with extrapolation into range of prematurity. (Gordon, Levine, *Am. J. Dis. Child.*, 52: 810, 1936.)

tend to produce the least amount of heat per unit of body surface, but also because it shows the amount of variation in determinations from the individual infants, and the variations in the results of one group of authors as compared with the results of others. Gordon and Levine's figures for the metabolism per kilogram of weight in prematures exceeded those of Talbot and his colleagues²² by 22 per cent, and were also above those of Marsh and Murlin,²³ and of Schadow,¹⁰ but the techniques of different investigators may well vary in one or more of the apparently minor details of routine, such

as the feeding of the infants or the regulation of their surrounding temperatures. The reason for mentioning these differences in results here is to stress the point that anyone carrying out metabolism studies on young and, particularly, premature infants, may perhaps compare his own results on individual subjects one with another more profitably than his averages with the averages obtained by other observers, unless the experimental conditions and techniques are kept absolutely similar.

In summary, what has been learned of fetuses, and of premature and mature newborn babies, indicates that life *in utero* is not a very active metabolic process and is one which, if terminated by an untimely and premature delivery, continues to require comparatively little energy for the basal functions of the body. After birth at full gestation the basal metabolism is a little nearer, but still considerably below that of the child and adult when considered in terms of comparative surface area. Since the newborn infant does not conform metabolically to surface specifications as to a natural law, there is reason to suppose that its heat production is controlled by some other regulator or requirement. This, Benedict and Talbot¹⁵ believed to be the active mass of protoplasmic tissue in the infant's body. They pointed out that not only the surface area but several other measurements of the body are roughly proportionate to the cube root of the square of the body weight; among these are the blood volume, the area of the trachea and aorta in section, and, perhaps, also the active protoplasmic mass. In any event, Benedict and Talbot decided that some other function than the simple surface cooling of a warmed body must be responsible for the rate at which metabolism proceeds, and the conception of the active protoplasmic mass appeared to them a much more logical regulating agency. In support of this reasoning they were able to select from their studies a number of infants which could be arranged in pairs of contrasting individuals whose surface areas were similar. One of each pair was a normal infant, well-grown for the age, while the other was in each case a more or less atrophic and poorly nourished infant who was some months the older of the two. In each pair, the latter member had much greater production of heat than the former, and although the latter had the same surface area as the former it must have had much less of fat and much more of "active protoplasm" in its body. The reasoning is complicated by age differences in metabolism; nevertheless, it has been a provocative and an appealing explanation of the regulation of metabolism.

Does the same reasoning apply to premature infants? With a notorious deficiency of fat, at least, as an insulation, premature

infants might be expected to have a comparatively large active protoplasmic mass, and therefore a comparatively larger heat production per unit of surface than do mature infants. That they actually display, on the contrary, somewhat lower energy metabolism is certainly explainable on grounds of qualitatively feeble protoplasmic processes and does not invalidate the probable quantitative importance of active protoplasmic mass. The theory is indeed borne out by the fact that the larger prematures weighing from 2.1 to 2.5 kilograms do have more heat production per unit of their surface than do infants born at term. On the other hand, Gordon, Levine and others²⁵ have made a strong argument against the value of drawing simple comparisons between metabolic rates of premature and mature infants, so that perhaps prematures can only be judged by other prematures.

Although basal heat production tends to rise rather steeply during the first year of life, ascending on the average from perhaps 27 calories/sq. m./hr. (or 1.75 per kg./hr.) at birth to nearly 50 calories/sq.m./hr. (or 2.4 cal./kg./hr.) at 18 months,¹⁷ there is little evidence of this tendency in the brief span of neonatal age. Murlin¹⁹ demonstrated a slight elevation at the ninth day, and says that another takes place about the fifteenth, but true basal levels are then more difficult to obtain. In the light of present data the tissues of an infant of two weeks might be expected to be about the same in basal metabolism as those of an infant one day after birth, although if more sensitive methods should become available the infant of three weeks might show some sign of greater basal activity. Differences between the sexes are without effect upon the metabolism not only in the neonatal period but until some time after infancy. Increasing muscular activity above the basal is of course a definite factor during the first few weeks.

It has been stated that measurements of respiratory gases give data as to the food being used for energy and that a third subject of major interest has been the collection and interpretation of such data. If protein is not being consumed in the body, the respiratory quotient (obtained by dividing volume of CO_2 produced by volume of O_2 utilized) will be a maximum of 1.0 during oxidation of carbohydrate material and will become a minimum of 0.71 if the material consumed be entirely fat. Consumption of protein would result in a respiratory quotient of about 0.8, but since, except under extraordinary circumstances, only a minor amount of bodily energy can come from that source, the respiratory quotient can be used largely as a tool for measuring the relative proportions of carbohydrate and of fat being oxidized.

Windle,²⁶ briefly, and Needham,⁴ at greater length, reviewed the data available from the mammalian embryo and concluded that the respiratory quotient tends to be near enough to 1.0 *in utero* to indicate an almost completely carbohydrate source of energy. Observations of this sort in human physiology are not possible, but the shorter the interval after birth at which a respiratory quotient can be obtained, the more properly may its evidence be applied to this aspect of fetal nutrition. Upon this point Benedict and Talbot's data from their newborn subjects¹³ are so authoritative as to make the review of any other work mainly of historical interest. Nevertheless, it may be worth while to mention a few other observations if only to show what wide variations have been reported and to indicate thus some of the difficulties of securing accurate data. Scherer²⁷ in 1896, concluded from observations on a large number of newborn infants that their respiratory quotients averaged about 0.7 and were actually as low as an average of 0.598 in the earliest hours of life. This figure he believed due to no ordinary type of food utilization, as indeed, it could not be, but to an "excess of anabolism over catabolism." Hasselbalch, who was apparently stimulated to some extent by this work to investigate the problem for himself, published in 1904 a series of careful observations⁵ which indicated a respiratory quotient close to 1.0 within the first hour or so after birth. Maintenance of this level, which indicated an exclusive utilization of carbohydrate, was only of short duration. By two hours after birth—and sooner in the cases of a few premature infants—the size of the quotient fell away to values between 0.80 and 0.85. Of course the conclusion was clearly that the newborn infant must be sustained by a store of carbohydrate existing probably as glycogen in its organs, and the implication was also that the fetus exists largely by consumption of substances of the same class. When carbohydrate was used up without immediate replacement after birth, its place appeared to be taken by fat.

Benedict and Talbot did not obtain respiratory quotients from any babies during the first hour after birth but made an impressive number of measurements within the first eight hours, as well as equally numerous ones on succeeding days. In the determinations made in earliest life the quotients averaged about 0.90; the results for the first eight days are here tabulated with similar data from Murlin and his colleagues. The table also includes calculation of the source of energy as shown by the first set of quotients when converted by the Zuntz-Schumberg tables¹⁶ into percentages of carbohydrate and fat being metabolized.

The impression given by these average figures should be qualified

by pointing out that there were rather striking individual variations, so that during the first few hours quotients as high as 1.00 and as low as 0.75 were obtained. The general conclusion of the authors¹³ was that "the results did not prove the existence of an excessive deposit of glycogen in the bodies of newborn children." Between the exhaustion of whatever glycogen is available during the first day and the appearance of an important secretion of milk

TABLE 23
RESPIRATORY QUOTIENTS IN NEWBORN INFANTS

Day of Life	Investigator		Per cent of Total Energy from:	
	Benedict-Talbot	Murlin, et al.	CHO	Fat
1st few hours	0.90		66	34
1	0.80	0.79	30.4	69.6
2	0.74	0.76	8	92
3	0.73	0.75	5	95
4	0.75	0.75	12	88
5	0.79	0.81	26.5	73.5
6	0.82	0.80	38	62
7	0.81	0.82	34	66
8	0.80	0.81	30.4	69.6

in the mother's breasts on or after the fifth day, is a period of low quotients indicating that the metabolic mixture being utilized is about 90 per cent fat.

Schadow¹⁰ and Schlossmann and Murchauser,¹¹ found respiratory quotients in general agreement with those listed in the table. Two prematures examined within a few hours after birth by Schlossmann and Murchauser had rather high respiratory quotients of 0.85 and 0.89, while others studied by Marsh and Murlin²³ on and after the third day remained at about 0.74 until a rather poorly sustained rise to 0.79 on the sixth. The influence of feeding is evident. Premature infants studied by Gordon and Levine²⁴ were apparently somewhat more freely fed than these and had respiratory quotients averaging about 0.88 during the first nine days of life and about 0.91 thereafter, while in a series of somewhat older prematures²² quotients toward the end of the first month of life reached an average of 0.96. For the most part these infants were being fed human milk; but such a quotient would mean that some 84 per cent of the metabolic mixture must be carbohydrate. In

general, the respiratory quotients of premature infants remain low for a longer portion of the first week than do those of mature infants, whereas later in the newborn period they appear to rise higher than do those of infants of full term. It would seem that after birth the premature may need to be kept in circumstances which will require him to subsist for a considerable period largely on his own body fat, whereas, once the first week or two are over, the premature absorbs and utilizes more energy from carbohydrate and less from fat than does the mature baby.

Investigations on a metabolic basis have thus given quantitative information as to the energy for unit of weight or surface which will be required to support the basal body activity shortly after birth, and have shown qualitatively which of the food elements seems to be drawn upon as most useful (or most available) as a source for this energy. Such data should be helpful in computing the dietary requirements best suited to the newborn period. For the basal processes, it has been stated that the average infant during the newborn period produces about 1.7 calories per kilogram per hour, and thus has a total 24 hour basal requirement for food which will yield about 41 calories per kilogram of body weight. The energy supply must further be increased to cover bodily activity and the calories lost in the feces, and, of course, after the first few days the growth requirements must be met. It is probably unnecessary to add further calories for the "specific dynamic action" of food in increasing metabolism, for, inasmuch as metabolism determinations on small infants have not been made in states of absolute fasting, some allowance for specific dynamic action is probably included in the basal data.¹⁷ Even so, many authors do compute an extra 10 or 15 per cent of the basal need and add it to the total for this purpose²⁸ although by the data of investigators who have measured this element¹⁹ such a percentage must be too large. However, its addition, plus a suggested amount for growth needs²⁹ results in the following itemized accounting:

TABLE 24
CALORIC REQUIREMENTS OF THE NEWBORN PERIOD

Basal metabolic need	41 calories per kilogram per day
+ 30% for bodily activity	12 calories per kilogram per day
+ 10% for fecal loss	4 calories per kilogram per day
+ 12% for specific dynamic action	5 calories per kilogram per day
+ Growth allowance	18 calories per kilogram per day

Total food requirement	80 calories per kilogram per day (36 calories per pound per day)
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Although the basal metabolism alters little, the neonatal period is one of increasing activity and, perhaps of increasing energy requirement for growth, so that 36 calories per pound will suffice for all needs only temporarily, and the energy allowance must become considerably higher within a very short time. The rapidity of this transition is well shown by the amount of food taken by the normal infant during each of the first few days. Simple measurements of this sort also offer an interesting check on the accuracy of predictions from calorimetric data. Faber,³⁰ by allowing a large number of infants to eat more or less to satiety from breast and bottle, found that by the fourth day of life the average infant took 90 calories per kilogram, or somewhat more than had been calculated as proper for its requirements, while by the eleventh day the average intake had risen to 117 calories per kilogram, or about 53 per pound.

The early work of Talbot, Sisson and others²² on the metabolism of premature infants emphasized the fact that the caloric intake of premature infants must reach a level very much above their basal energy requirements—even two and a half times the basal—before gain in weight can occur. This meant an intake of as much as 150 calories per kilogram (nearly 70 per pound), an amount which was necessitated by an extremely large quota of calories required for growth, according to the authors' proposal. They were not impressed by the amount of food lost in the feces, and they decided that the allotment for muscular activity should be only some 10 per cent of the basal. A somewhat different conception is shown in the more recent work of Gordon, Levine and their associates²⁵ who found that after the age of two weeks premature infants would meet the primary specification of proper nutrition (by gaining weight) on 120 calories per kilogram, or 55 per pound; indeed these authors surmise that at a still younger period the premature might be made to gain on an intake of even less energy than this. The premature infant was shown in Gordon's work to be particularly wasteful of dietary calories from fat, since caloric losses in the feces amounted to as much as 32 calories per kilogram, most of which consisted of unabsorbed fat. This amount is very much greater than the 5 or 10 calories per kilogram lost by larger infants in this way. It is not as yet possible to be didactic as to the exact caloric specifications required by premature infants, since there continues to be discussion as to whether the largest gain in weight and the optimum gain in weight can be looked upon as synonymous terms.

BODY TEMPERATURE

Since the body's metabolism is expressed in terms of production of heat and since the thermometric reading of body temperature is the simplest way in which heat presents itself for clinical consideration, the temperature of the newborn infant may be discussed here. In general, the type of heat production which has been largely considered in the foregoing pages should be called chemical, representing as it does the release of energy in the form of heat as a product of chemical reactions. Alterations in the amount of such processes thus form the *chemical* regulation of temperature. Associated with this and sometimes affecting it are another group of processes which go to make up the *physical* regulation of temperature. Under this heading are shivering and other forms of bodily activity tending to increase heat production, vasoconstriction of surface vessels tending to conserve heat, and perspiration and surface vasodilatation tending to the reverse action of disseminating heat which is unwanted. The two types of regulation complement one another, the chemical being, in the simile of Dr. Gamble, like the coarse adjustment of a microscope, which places temperature economy within certain general limits, while the physical processes are necessary as a fine adjustment for the more delicate regulation to that narrower range which makes for greater bodily comfort and more efficient physiological activity. In general, when the physical regulatory processes are not adequate to preserve thermal stability, the strongest available chemical regulations will not serve to maintain constant body temperature. As physical mechanisms become more responsive with increasing age of the human infant, chemical regulation is called upon less, and the thermal conditions of the body become much more constant.³¹

The effects of external temperature variations might be simply to decrease or increase chemical heat production, as simple chemical reactions progress less actively in cold solutions and more rapidly over a Bunsen burner. Thus Benedict and Talbot¹³ state that "there is a distinct correlation between the body temperature of the infant and the total metabolism, for on the days with low body-temperature the metabolism was also low. . . . On the first day, when the low temperatures predominate, we find likewise a somewhat lower metabolism per kilogram of body-weight and per square meter of body surface." On the other hand, as the same authors proceed to point out, physical regulation may be called forth by a cool environment and thus

—provided this sort of regulation is adequately developed—shivering, increased muscular activity, and increased heat production will follow, so that cooling may lead either to less or, secondarily, to more heat production.

Of most interest as phases of body temperature adjustment in newborn life are the normal variations following birth, the relationship of the infant's temperature to that of its surroundings, the relationship between external and internal (or skin and rectal) temperatures, the particular effects of premature birth upon body temperature, and finally the presence or absence of any diurnal temperature rhythms in neonatal life. These aspects will be considered in the order given.

Body temperature control is a function of heat production and of heat loss. It is obvious from the variable nature of heat production repeatedly stressed in the foregoing discussion of metabolism that the first of these factors cannot be expected to behave in a very reliable fashion in the newborn. Nor can any better regulation be expected upon the side of heat loss or conservation. The demands of surface area, the immaturity of sweating and shivering mechanisms, the probable disadvantages of delicate skin and meager subcutaneous fat, all are very apparent handicaps to controlling both the rate of heat loss and the degree of loss itself. Thus interest is not so much in the *fact* of neonatal temperature instability as in the *degree* of instability which can be considered normal, and in the possibility that variations beyond that degree will be harmful to newborn patients.

The temperature of the infant at birth is the same as (or perhaps very slightly more than) that of its mother. How great a decline would occur thereafter if the infant were then left uncovered for very long as amniotic fluid evaporated from its skin at an ordinary room temperature does not appear from the literature. Some immediate temperature fall always occurs in spite of protection against it. The standard practice of the Boston Lying-in Hospital is to wrap newborn infants at once in one or two blankets and then to place them in a nursery the temperature of which is kept at 80 to 85 degrees F. Here the temperature of the infant is taken rectally every hour until, at from six to ten hours, it has risen to maintain a fairly steady level. The infant is then bathed, dressed, and taken to another nursery. The hourly rectal temperatures of an unselected series of twenty normal babies so cared for during the immediate post-natal period are shown graphically in Figure 23. The patterns followed by a few individual ones have been traced by connecting lines. The average level one hour after birth is 95.8 degrees, or a

decline of about 3 degrees F. (1.8° C.) from what must have been the original temperature at emergence from the birth canal. Sometimes the first hour or two may witness a fall as great as 5° F. (2.8° C.), without any marked disturbance of environmental temperature or nursery routine to provide an explanation. The average hourly rise thereafter is a smooth enough one but it is compounded from wide individual variations.

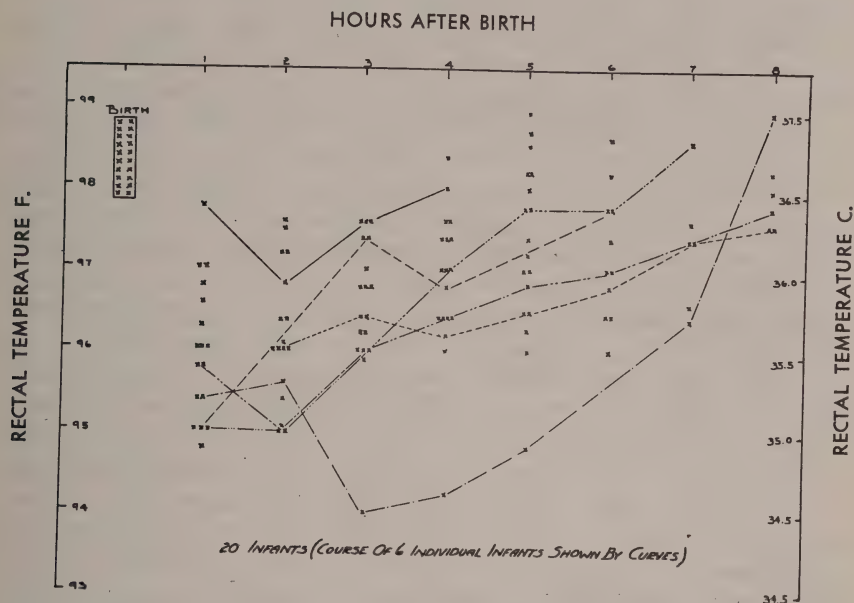


FIGURE 23

Bodily temperatures of 20 normal infants during the first 8 hours after birth under routine conditions. The courses of certain individual infants are shown by connecting their hourly temperature measurements. Birth range is that observed in normal women at delivery.

Speculation as to whether this post-natal three degree temperature fall is evidence of immaturity of temperature centers or whether the same thing might be expected from an older infant treated to the same general thermal experiences is a little academic, but there is some reason to believe the former explanation is probably at least partially true. To explain the early inability to resist changes in environmental conditions, Brock³² uses the term "lack of practice" (*Ungeübtheit*) rather than "immaturity" of anatomical mechanisms. So quickly does the ordinary infant improve in this fundamental physiological performance of temperature stability

in the face of environmental variation that Brock's interpretation may probably be a correct one. If anatomical maturity were required for temperature stability, such a maturation must occur extremely rapidly. Newborn *premature* infants, however, must certainly meet environmental temperature variations with both lack of practice and anatomical immaturity, as will be discussed below.

Although the reaction of the infant to this temperature fall immediately after birth does not seem to have been studied, several investigators have carried out experiments on infants slightly older but still in the neonatal period. More than fifty years ago Raudnitz³³ made an extensive research from which he concluded that the stronger and "better developed" was an infant, the more quickly its temperature would return to normal after an artificial chilling. As a corollary it was also noted that whereas a strong baby might react promptly to a cool bath on the day of birth, a weaker infant might not be able to react in equally good fashion until the fourth or fifth day of life. These facts could be demonstrated in the same subject. On the first day of life an infant was immersed in a bath at 25° C. (77° F.); 80 minutes later its temperature was 35.1° C. (95.2° F.). The same procedure was repeated on the second day of the same baby's life, and at this time the infant's temperature only 50 minutes after the bath had risen to 36.9° C. (98.4° F.). Raudnitz was convinced by his observations that well-developed babies were able to shiver on the first day of life, whereas weaker ones did not acquire that reaction until several days later. Eroess³⁴ demonstrated much the same findings in somewhat older infants, while Mendelsohn³⁵ and later Blackfan and Yaglou³⁶ brought about a further degree of understanding by following both surface and internal (rectal) temperatures during and after cooling and warming periods.

The investigations of Blackfan and Yaglou throw considerable light on the way in which premature infants respond to external temperature changes in comparison with the behavior of "mature" infants under the same conditions. Two figures from their monograph are reproduced here. In the first (Fig. 24) is shown the effect of raising the room temperature from 80° F. (26.7° C.) to 100° F. (37.8° C.). The normal infant whose performance is recorded at the bottom of the diagram was eleven weeks old. Although its skin (cheek) temperature began to rise at once with that of its environment and increased during 3½ hours by almost 6 degrees F., the rectal temperature held fairly level for 1½ hours and then rose only 2.3° F. (1.3° C.). On the other hand the skin and rectal temperatures of the two premature infants (aged 1½ and 9 weeks) rose in almost

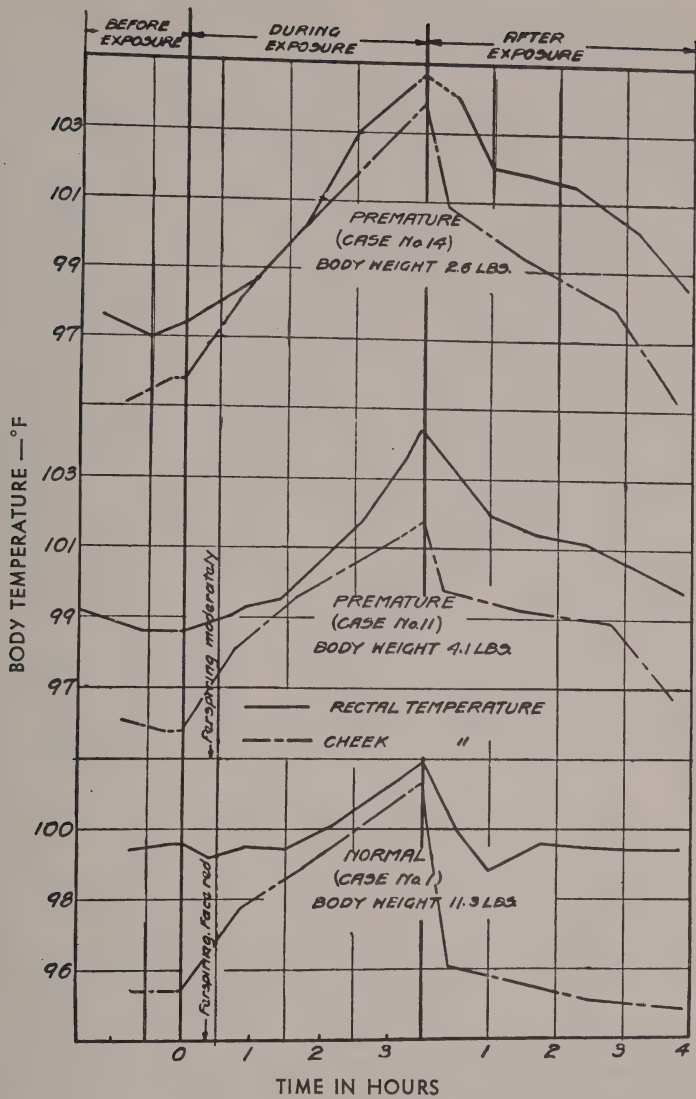


FIGURE 24

Effect of raising the environmental temperature from 80° to 100°F. upon the external and internal temperatures of two premature infants and one of full-term gestation. Note the much larger alteration in internal temperatures of the immature as compared with the mature infant. (Blackfan, Yaglou. *Am. J. Dis. Child.*, 46: 1175, 1933.)

simultaneous and parallel fashion, those of the smaller and younger subject reaching an almost identical peak, which was an elevation of 7.3° F. (4° C.) for the rectal and 8° F. (4.4° C.) for the skin temperatures. The larger and older full-term baby was much better able to defend the stability of its internal temperature, a process in which sweating and superficial vasodilatation were brought into use. Only one of the premature infants appeared able to call upon these mechanisms, and even so they were ineffectually used. Moreover, it will be noted from the chart that upon return to a normal environment the rectal and skin temperatures of the mature infant became readjusted much more rapidly and correctly than did those of the prematures.

In Figure 25 are shown the results of a similar experiment in which room temperature was lowered for four hours to 63° F. (17.2° C.). The normal infant studied was five weeks old. Its skin cooled rapidly with the environment, but motor and vasomotor changes tending to increase and to retain body heat functioned so efficiently that the rectal temperature at first actually rose, and thereafter declined only very slowly. The skin and rectal temperatures in the two premature infants showed the usual tendency to a parallel response, although in the larger premature the defense against cooling seemed slightly stronger than that exhibited against heating as shown in the preceding chart. The smaller premature baby became cyanotic and was removed to a warmer room. It had shown no shivering nor evidence of vasomotor conservation of surface heat.

The essentials of body temperature control could scarcely be more clearly demonstrated than by these diagrams, nor could better testimony be presented as to the shortcomings of the premature infant in this regard. It is probable that if such data were available for full-term infants during the first days of life, a degree of response somewhere between the comparatively inefficient performances of these prematures and the satisfactory ones of the other infants would be demonstrated.

There is need of convincing data, rather than opinion, as to the harm done premature infants by subnormal body temperature and to the manner in which this damage is brought about. Eckstein³⁷ did not believe from his observations that much harm does occur from this cause nor indeed that premature infants are so defenseless against environmental changes as Blackfan and Yaglou's charts have since indicated. Eckstein's statement that premature infants are not lacking in defense reflexes such as vasomotor reactions, shivering, and perspiration has not been confirmed. His data do

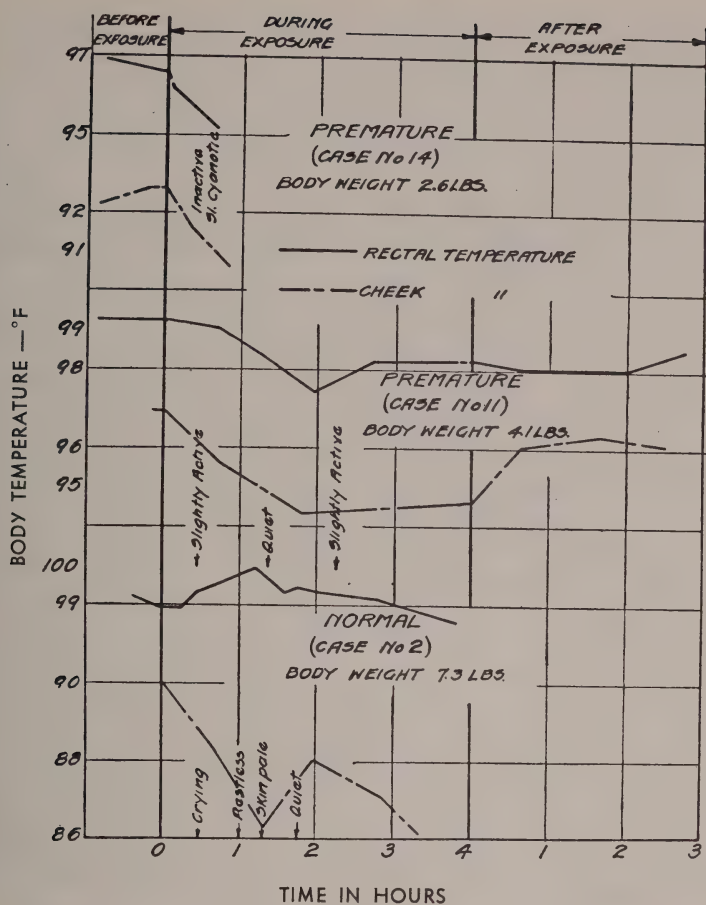


FIGURE 25

Effect of lowering environmental temperature from 80° to 63°F. Compare with Figure 24. (Source same as Figure 24.)

show that a very low temperature at the time of hospital admission of a premature infant need not imply a necessarily fatal outcome. Of 21 infants whose admission temperature ranged from 93.2° F. (34° C.) down to 78.8° F. (26° C.) only 6, or about 29 per cent, failed to survive. The necessary upswing from these low admission temperatures did not always require an extremely warm environment; some infants seemed able to raise their body temperatures above that provided by the surroundings. Thus a baby weighing 2 lb. 10 oz. (1200 g.), and admitted with a body temperature of 78.8° F. (26° C.) on the first day of life, had reached a body temper-

ature of 99° F. (37.2° C.) ten hours later in a warming cradle the temperature of which was 91.4° F. (33° C.). Such good results do not appear in the material collected by Yllpö,³⁸ although it is pointed out that many of these latter patients had evidence at autopsy to show that their major difficulty may have been from birth trauma rather than from low temperature *per se*.

Observations which lend partial support to Eckstein's lack of concern over low temperatures in premature subjects have been made during more recent years at the Infants' Hospital in Boston. Here the former custom of attempting to stabilize the body temperature of premature infants at or near 98.6° F. (37° C.) has been to some extent relaxed. The current practice has become one of first overcoming the initial cooling usually present at admission, by warming the infant to 97–99° upon arrival, but thereafter allowing its temperature (in an environment of 85° F.) to drift towards whatever lower level it can maintain with stability. Thus, it is not uncommon for the smaller ones among these patients to live for many days or even some weeks at levels of 93° F. (34° C.) or less, after which, and without alterations in their surrounding environment they gradually increase in body heat until a plateau of about the adult normal value is reached. This entire course of temperature adjustment takes place in a nursery of constant temperature and humidity. Unless some such stabilized environment is available it would be dangerous to allow the infant this chance to seek its own temperature level; indeed no constant level would probably be attained under such circumstances. Other things being equal, it might be of considerable advantage to an infant to exist at a "subnormal" temperature, as the metabolism, and thus the food requirement and the digestive and assimilative processes would be reduced under such conditions.³⁹ Moreover, the infant might benefit by the thermal economy resulting from a smaller differential between rectal and surface temperatures.

In spite of this and of Eckstein's observations, it would seem best to allow the adjustment of body temperatures at "subnormal" levels only after premature infants had been warmed to overcome the initial postnatal cooling. In other words, the premature infant may tolerate a temperature of 93° at two weeks of age whereas prolonged cooling of the same degree could be dangerous during the first day after birth, when so many adjustments are being demanded by abandonment of intra-uterine life. It is obvious that the smaller and younger the organism, the less will its body temperature maintain uniformity under too warm an environment, so that premature infants often overshoot the desired mark when too

much heat is afforded them by mechanical devices or even by too many wrappings. Thus a rise of several degrees above the proposed "normal" may follow the injudicious use of hot water bottles or blankets. The program of allowing stabilization at "subnormal" temperatures does prevent this type of useless and perhaps harmful fluctuation.

The characteristics of neonatal life with regard to diurnal temperature rhythms have been studied by Kleitman and others⁴⁰ and more elaborately by Jundell.⁴¹ It is well known that a rhythm occurs in the adult temperature by virtue of which, according to Jundell, the day temperature may be 1.5° F. (0.8° C.) above that of the night, while in children between two and five years this normal fluctuation is even greater, swinging as much as 1.8° F. (0.95° C.). The basis of this variation is, of course, most probably one of differences between nocturnal and diurnal metabolic and bodily activity. Jundell found that whereas a large number of infants did show a daily temperature rhythm late in the first week (not dependent upon feeding or other schedules) the fluctuations were extremely small ones so that the mean of temperatures between 4 A.M. and 4 P.M. was only 0.18° F. (0.1° C.) greater than the mean for the other twelve hours. Although obviously requiring a fairly stable environmental temperature, this monothermic character of neonatal life must be due to the equal distribution of body activity (or inactivity) throughout all the twenty-four hours. The younger the infant, the more is its time occupied by sleeping; given proper surroundings the premature infant is for the same reason still more apt to have a monothermic temperature curve, at least speaking in terms of diurnal variations, than is the full term infant.

CLINICAL SUMMARY

The infant emerges from a state of low heat production during fetal life to a neonatal period in which *minimal* or *basal metabolism* appears to be less active than that of the adult and considerably below that of the child. A comparison, properly made on a basis of surface area, places the heat production during the neonatal period at about two-thirds of the adult performance. The upper and lower limits of basal metabolism are so widely separated that other and more complicated formulae than those for surface area have been proposed for arriving at the normal; these have been discussed earlier in this chapter. The metabolism of prematures tends to be lower, in proportion to surface, than that of infants born at term, and this discrepancy is greatest in the smallest prematures. The activity of crying and kicking may increase heat production and

therefore elevate the caloric requirement by 100% or more above minimal values, this increase being larger in the more mature and robust infants.

From *respiratory quotients* it is clear that the source of fetal and immediate post-natal energy is carbohydrate and that a substitution of fat to meet this purpose occurs by the third day, whereas a metabolic mixture of one-third carbohydrate and two-thirds fat is utilized by the end of the first week. Premature babies subsist for a longer post-natal period upon their body fats, but once milk becomes available in substantial amounts the premature subject shows a respiratory quotient indicative of greater dependence upon carbohydrate and less upon fat than does the full-term baby.

From all of these studies a caloric basis can be established for the feeding of newborn babies. The fundamental principles are as follows: (1) Life processes utilize a relatively small number of ingested (or other) calories until growth begins. (2) Active babies consume definitely more energy than somnolent ones. (3) The caloric allowance for all needs except growth can be met by about 62 calories/kg. or 28/lb./day; the addition of a component for growth brings the figure up to about 80 calories/kg. or 36/lb./day. (4) The fact that a hungry and thriving infant of 10 to 14 days will actually consume somewhat more than 115 calories/kg. or 53/lb./day is not to be taken as a rule for feeding every baby at this time. (5) The infant lives mainly on stored fat until milk can be ingested and digested. (6) In prematures, with smaller fat reserves and less powers of assimilation, the requirements of metabolism, activity, and growth are sufficiently low so that the available fat is consumed over a rather longer interval. When external sources of energy become available, the premature tends to reject fat, or at least to utilize carbohydrate to a greater degree than does the full-term baby. (7) The premature infant can gain weight upon as little as 120 calories/kg. or 55/lb./day; need for more should arouse suspicion that fat is being wasted in the stools.

The *body temperature* at birth is the same as the mother's, but even though the infant is wrapped and placed in a warm room it undergoes an immediate loss of some 2° to 5° F., after which a rising trend sets in which carries the temperature up to 98° to 99° in about 8 hours. Both chemical and physical means of temperature regulation are qualitatively and quantitatively imperfect in all newborn infants, the inadequacy of physical factors being most evident in premature babies, whose extensive surface, scanty subcutaneous fat, poor vasomotor control, and inadequate sweating and shivering

reactions place them at a considerable disadvantage. In these subjects, any change of surface temperature is promptly followed by a parallel change of internal temperature.

Since the outstanding difficulty is thus one of stability of body temperature, it is probable that a premature infant whose temperature remains steady at a level somewhat below the usual adult normal is being better cared for than one whose temperature fluctuates widely about an average of 98.6° F. Before any infant is allowed to seek its own temperature level in this way, it should be warmed to 98° to 99° F. as a starting point, and an environment which varies little in heat and humidity should be provided.

BIBLIOGRAPHY

1. BOHR, C.: Der respiratorische Stoffwechsel des Säugethierembryo, Skand. Arch. f. Physiol. 10: 413, 1900.
2. MURLIN, J. R.: The metabolism of development. I. Energy metabolism in the pregnant dog, Am. J. Physiol. 26: 134, 1910.
3. CARPENTER, T. M., and MURLIN, J. R.: The energy metabolism of mother and child just before and just after birth, Arch. Int. Med. 7: 184, 1911.
4. NEEDHAM, J.: Chemical Embryology. Vol. 2. New York, The Macmillan Company, 1931.
5. HASSELBALCH, K. A.: Respirationsforsøg paa nyfødte børn, Bibliotek f. Laeger (8th Ser.) 5: 219, 1904.
6. COHNSTEIN, J., and ZUNTZ, N.: Untersuchungen über das Blut, den Kreislauf, und die Athmung beim Säugethier-Fötus, Arch. f. d. Ges. Physiol. 34: 173, 1884.
7. BARCROFT, J.: Fetal circulation and respiration, Physiol. Rev. 16: 103, 1936.
8. BARCROFT, J., KENNEDY, J. A., and MASON, M. F.: Direct determination of oxygen consumption of foetal sheep, J. Physiol. 95: 269, 1939.
9. HASELHORST, J., and STROMBERGER, K.: Über den Gasgehalt des Nabelschnurblutes vor und nach der Geburt des Kindes und über den Gasaustausch in der Plazenta . . . Ztschr. f. Geburtsh. u. Gynäk. 102: 16, 1932.
10. SCHADOW, H.: Der Betriebsstoffwechsel und Kalorienbedarf frühgeborener Säuglinge, Jahrb. f. Kinderh. 136: 1, 1932.
11. SCHLOSSMANN, A., and MURSCHEHAUSER, H.: Gasstoffwechseluntersuchungen bei Neugeborenen und Frühgeborenen, Ztschr. f. Kinderh. 54: 301, 1933.
12. LOEWY: cited by Haselhorst and Stromberger; see 9 above.
13. BENEDICT, F. G., and TALBOT, F. B.: The Physiology of the Newborn Infant. Character and Amount of the Katabolism. Washington, Carnegie Inst., 1915. Carnegie Inst., Pub. No. 233.
14. GRIFFITH, J. P. C., and MITCHELL, A. G.: Textbook of Pediatrics. 3d ed. Philadelphia, W. B. Saunders, 1941.
15. BENEDICT, F. G., and TALBOT, F. B.: The Gaseous Metabolism of Infants, with special reference to its relation to Pulse-rate and Muscular Activity. Washington, Carnegie Inst., 1914. Carnegie Inst., Pub. No. 201.

16. DuBois, E. F.: *Basal Metabolism in Health and Disease*. 3d ed. Philadelphia, Lea and Febiger, 1936.
17. Benedict, F. G., and Talbott, F. B.: *Metabolism and growth from birth to puberty*. Washington, Carnegie Inst., 1921. Carnegie Inst., Pub. No. 302.
18. Feldman, W. M.: *The Principles of Ante-natal and Post-natal Child Physiology Pure and Applied*. London, Longmans, Green & Company, 1920.
19. Murlin, J. R., Conklin, R. E., and Marsh, M. E.: Energy metabolism of normal new-born babies, with special reference to the influence of food and of crying, *Am. J. Dis. Child.* 29: 1, 1925.
20. Levine, S. Z., and Marples, E.: Respiratory metabolism in infancy and childhood; biometric study of basal metabolism in normal infants, *Am. J. Dis. Child.* 41: 1332, 1931.
21. Talbot, F. B., Sisson, W. R., and others: The basal metabolism of prematurity. II. Relation of basal metabolism to caloric intake and weight curve, *Am. J. Dis. Child.* 24: 95, 1922.
22. Talbot, F. B., Sisson, W. R., Moriarty, M. E., and Dalrymple, A. J.: The basal metabolism of prematurity. III. Metabolism findings in twenty-one premature infants, *Am. J. Dis. Child.* 26: 29, 1923.
23. Marsh, M. E., and Murlin, J. R.: Energy metabolism of premature and undersized infants. *Am. J. Dis. Child.* 30: 310, 1925.
24. Gordon, H. H., and Levine, S. Z.: Respiratory metabolism in infancy and in childhood; respiratory exchange in premature infants-basal metabolism, *Am. J. Dis. Child.* 52: 810, 1936.
25. Gordon, H., Levine, S. Z., Deamer, W. C., and McNamara, H.: Respiratory metabolism in infancy and in childhood; daily energy requirements of premature infants, *Am. J. Dis. Child.* 59: 1185, 1940.
26. Windle, W. F.: *Physiology of the Fetus; Origin and Extent of Function in Prenatal Life*, Philadelphia, W. B. Saunders, 1940.
27. Scherer, Fr.: *Die Respiration des Neugeborenen und Säuglings*, *Jahrb. f. Kinderh.* 43: 471, 1896.
28. Marriott, W. M.: *Infant Nutrition*. 2nd ed. St. Louis, C. V. Mosby, 1935.
29. Holt, L. Emmett, and Howland, J.: *Holt's Diseases of Infancy and Childhood*. 11th ed. New York, Appleton-Century, 1940.
30. Faber, H. K.: Food requirements in newborn infants; a study of the spontaneous intake, *Am. J. Dis. Child.* 24: 56, 1922.
31. Babák, E.: Ueber die Wärmeregulation bei Neugeborenen, *Arch f. die Ges. Physiol.* 89: 154, 1902.
32. Brock, J., Thomas, E., and Peiper, A.: *Biologische Daten für den Kinderarzt; Grundzüge einer Biologie des Kindesalters* 2 Bd. Berlin, J. Springer, 1934.
33. Raudnitz, R. W.: Die Wärme-regelung beim Neugeborenen, *Ztschr. f. Biol.* 24: 423, 1888.
34. Eröss, J.: Untersuchungen über die normalen Temperatur-Verhältnisse der Neugeborenen, *Jahrb. f. Kinderh.* 24: 189, 1886.
35. Mendelssohn, A.: Beobachtungen über Hauttemperaturen der Säuglinge, *Ztschr. f. Kinderh.* 3: 292, 1911-12.
and, Über das Wärmeregulations-vermögen des Säuglings, *Ztschr. f. Kinderh.* 5: 269, 1913.

36. BLACKFAN, K. D., and YAGLOU, C. P.: The premature infant; a study of the effects of atmospheric conditions on growth and on development. *Am. J. Dis. Child.* 46: 1175, 1933.
37. ECKSTEIN, A.: Über die Wärmeregulierung der Frühgeburten, *Ztschr. f. Kinderh.* 42: 5, 1926.
38. (a) YLPPÖ, A.: Pathologisch-anatomische Studien bei Frühgeborenen. Beiträge zur physiologischen, pathologischen und sozialen Hygiene des Kindesalters, *Ztschr. f. Kinderh.* 20: 212, 1919.
- (b) YLPPÖ, A.: Zur Physiologie, Klinik und zum Schicksal der Frühgeborenen, *Ibid.* 24: 1, 1920.
39. KROGH, A.: Die quantitative Beziehung zwischen Temperatur und Standardstoffwechsel bei Tieren, *Ztschr. f. physik-chem. Biol.* 1: 491, 1914.
40. KLEITMAN, N., TITELBAUM, S., and HOFFMAN, H.: The establishment of the diurnal temperature cycle, *Am. J. Physiol.* 119: 48, 1937.
41. JUNDÉLL, I.: Über die nykthemeralen Temperaturschwankungen in dem ersten Lebesjahr des Menschen, *Jahrb. f. Kinderh.* 59: 521, 1904.

Chapter VIII

THE PHYSIOLOGY OF THE DIGESTIVE TRACT

Section 1 . . . Functional Anatomy

Section 2 . . . Fetal and Neonatal Digestive Secretions

Section 3 . . . Clinical Summary

FUNCTIONAL ANATOMY

THE DIGESTION and absorption of food is, like the respiration of air, a function which the infant has had no opportunity of practicing during its fetal career. The circulation of blood, the assimilation from the blood of food substances for growth, and the formation of urine are activities which have been to a greater or less extent either assumed or attempted by the organism *in utero*. But the gastrointestinal tract has had only slight opportunities for utilizing its muscles and practically none at all for exercising its chemical and absorptive powers. Moreover, although this is the state of affairs until birth, by as little as two weeks thereafter the digestive tract must be able to process an amount of raw material which is proportionately very large when compared with the intake of an adult organism. Thus, during the 24 hours following birth an infant's gastrointestinal tract usually has no work to do beyond setting out to clear itself of meconium, but two weeks later it must handle about 18 ounces (540 cc.) of milk, and indeed may deal adequately with as much as twice that amount.¹ Computed in accordance with the relative body surfaces this would be the equal of a daily intake of from four to eight quarts (or liters) of milk by an adult; on a perhaps more justifiable basis of comparative body weights it represents from 10 to 20 quarts.

Before discussing the digestive enzymes concerned in this undertaking and the way in which the individual food substances are conveyed through the intestinal wall, a description of the anatomy and motility of the gastrointestinal tract at this time may be useful. During the last two months or so of fetal life the digestive apparatus is obviously capable of the same general degree of motor activity as it can perform at the time of normal birth. Not only is this apparent from the successful performance of infants born before term; it also has been shown by various observations that cer-

tain gastrointestinal movements are carried out *in utero*. Many substances present in the meconium must have come there by being swallowed. Windle, who has himself made several contributions to the subject, has reviewed the literature in his book on the fetus.² In animal experiments the fetus has been shown to ingest dyes and other substances introduced into the amniotic fluid and later identified in the fetal circulation, urine and tissues.^{3,4} Indeed the fetal swallowing of saccharine-flavored amniotic fluid has been used with some success as a means of reducing hydramnios in human mothers.⁵ Studies such as these, and more recent ones utilizing radio-opaque solutions, have shown that the fetus swallows amniotic fluid by as early as the fifth month of uterine life,⁶ and probably even before that. Henderson⁷ quotes Hooker's finding of amniotic fluid (which must have been swallowed) in the stomach of a fetus aged only 15½ weeks.

Both gastric and intestinal peristaltic movements have been demonstrated in animal and in human fetuses about as early as has swallowing^{2,6,8} and hunger contractions can appear in the stomach of human infants at birth if not before.⁹ The ingestion of surrounding material and its propulsion through the intestinal tract become more active and rapid as the end of gestation nears. Changes in fetal peristalsis also occur when the organism is subjected to increasing anoxia; in the bowel of the anoxic fetus there occurs a tendency to segmentation rather than to "digestive" peristalsis; as the stimulus becomes more severe this is replaced by irregular and agonal movements probably accounting for the passage of meconium which takes place in the human fetus under asphyxial circumstances. There is doubt as to whether the human fetus passes meconium *in utero* under any normal circumstances, although this is a normal pre-natal function in certain animals.⁸

Mathematical measurements of visceral size and capacity are of little practical importance, though it has been pointed out that the intestinal tract at birth is of greater length in proportion to the length of the body than is the case in adult life, a disproportion which is even more marked during the second year of infancy.¹⁰ Measurement of the neonatal gastric capacity has been a favorite study of earlier observers,¹¹ but not until the development of roentgenological techniques was it apparent how futile such estimations are when applied to a viscus capable of such extreme dilatation as is the infant's stomach, and of such unpredictable variability in its rate of emptying. The anatomical capacity has usually been decided upon as between 30 and 60 cc. at birth, but this has little to do with the function of an organ which is not only able on occasion

to stretch to several times its usual size but also to adjust its content by emptying some or all of it into the duodenum. The cross-sectional anatomy of the stomach wall may be of a little more significance. The general consensus is that all the glandular elements found in the gastrointestinal mucosa of adults are present at birth, though glandular structures are more shallow and are especially so at premature birth. The gastric musculature, according to Scammon,¹¹ is somewhat deficient, particularly in the longitudinal fibers over part of the greater curvature. The neonatal intestine shows the same disproportion in the relatively greater thickness of mucosa as compared to muscle. Gundobin¹² states that the ratio of mucosa to muscle in the newborn subject is as 23 to 26, whereas in the adult the ratio is as 27 to 41. The duodenal musculature at birth, according to the same author, is no thicker than that of the jejunum, while on the other hand, the wall of the colon is relatively better developed than that of the small bowel. Elastic fibers are more or less deficient throughout the intestinal submucosa at birth, but the digestive and absorptive surfaces of the intestine in the newborn are completely developed and, according to Gundobin, not different in cellular elements or size from the same structures in the adult.

Because of the conditions described above, and because of the relatively greater length of the bowel at birth than after full growth of the body, the newborn infant should be anatomically able to absorb food quickly and easily. Further, the infirmity of supporting structures ought to and does allow considerable distension to occur, and makes for a great variability of organ size and topography under physiological and pathological conditions. Some irregularities of peristaltic activity might also be predicted. These are among the outstanding characteristics which have been brought out by roentgenologic studies of the gastrointestinal tract in action.

Here one is grateful for the complete and careful studies of Henderson, who has recently reviewed the more significant contributions in the literature,¹³⁻¹⁸ and presented his own experience with gastrointestinal tract examinations after the oral administration of barium to over a hundred normal infants aged between two and nine days and after the introduction of barium directly into the upper bowel of other infants by the duodenal tube.⁷ In another communication Henderson and Briant have described the roentgenology of the colon after barium enemata in infants of comparable age.¹⁹ Perhaps the most important generalization that can be drawn from such studies is that no uniformity is to be expected. So wide is the range of normal that dogmatic descriptions become

unwarranted, and attempts at anatomical classification of findings result in too many categories for very profitable application. Thus, the various gastric configurations encountered roentgenologically have been graphically identified as *scaphoid*, *modified fish-hook*, *retort*, *tobacco-pouch*, and *steer-horn*, and still other equally vivid classes have been added. While most neonatal stomachs could be described as presenting some one of the latter three forms, a more satisfactory observation might be simply that the variations of shape in the stomach at birth are probably greater than in children or adults.

Even more may this be true of size as observed roentgenologically. Under ordinary (non-obstructive) circumstances distension occurs especially from the swallowing of air with the food; "when the infant cries during feeding, large amounts of air are swallowed, and the stomach may become easily four or five times the size seen when only a two ounce barium meal is present."⁷ Indeed, Thiele²⁰ states that the size of the infant's stomach after a meal depends not on the amount of food but on the amount of air swallowed. This, with changes in bodily posture, leads to considerable variations in the position (as well as in the amount of space) occupied by the stomach in the abdominal cavity of any individual infant. The greater curvature may lie at any level from the eighth thoracic to the fourth lumbar vertebra when the infant is held upright,^{7,21} although it is most commonly at the twelfth thoracic or first lumbar.

The considerable variations in the muscular activity of the stomach, repeatedly demonstrated by barium studies, have shown no consistent relationship to the size or composition of the meal, the amount of air in the stomach, or the bodily activity of the infant. It may be stated in a general way that peristaltic movements of the stomach are less frequent than in older infants or adults. Bouslog and his colleagues¹⁷ took films at two, five and ten minutes after feeding was begun in ten infants, and then at repeated thirty minute intervals. In 137 films so taken, only rarely were peristaltic markings discernible. Such activity seldom occurs during sleep, but gentle massage over the abdomen commonly produces some peristalsis⁷ and a stomach which has been caused to contract by regurgitation of a large quantity of air may show more evident peristaltic movement thereafter. On the other hand the presence of the air bubble seems to exert no regular influence on the time of emptying.¹⁷ Passage of the meal from the young infant's stomach would, in fact, appear to be associated more with unpredictable relaxation of the pylorus and massive, gentle, non-peristaltic move-

ment. Henderson sums up his considerable experience with the newborn in these sentences: "Motility (of the stomach) is much more variable than in adults. During the period of taking the meal from a bottle emptying time is often rather rapid. Then a period of an hour or more may elapse in which no motility worthy of mention occurs. This may be followed by active peristalsis with evacuation of a large part of the remaining barium. Following this a period of rest often ensues and the residual meal shows only slight change in amount for several hours. On the other hand, some infants exhibit no gastric peristalsis and no motility during the feeding, nor for perhaps an hour thereafter. Yet the final emptying time may be actually shorter than in infants whose stomachs begin to empty immediately. As a rule, the greatest amount of emptying takes place during the first one and one-half to two hours after the meal."

The stomach empties more slowly in the newborn period than at any other time of life, and this is especially true when complete evacuation of a meal is meant, though the major portion usually does leave the stomach in less than three to four hours. In many newborn infants a considerable amount is said to remain at eight hours, and Henderson mentions the frequency with which he found barium still present 24 hours after feeding. In one case some barium lingered for seven days! Other authors¹⁷ whose material included infants of from one week to six months of age found that the emptying time was less than five hours in 30 per cent, 5 to 8 hours in 27 per cent and more than 8 hours in the remaining 43 per cent of normal subjects. The interesting observation was made in a few infants who were fed a standard formula (without barium) 4 hours after the barium meal, that the introduction of the second feeding caused portions of the first to remain somewhat longer in the stomach than if a second feeding was withheld pending complete departure of the foregoing one. Of 5 premature infants ($4\frac{1}{4}$ to $4\frac{1}{2}$ pounds in weight) a larger percentage had empty stomachs in five hours than was the case in babies born at full term. Data from smaller prematures would be interesting.

Before roentgenological techniques were developed, it was shown²² that human milk leaves the stomach somewhat more rapidly than cow's milk, though cow's milk which has been boiled does not remain so long as when it is fed in its natural state.²³ In any diet ordinarily prescribed for the newborn, no important effect is to be assigned to any one constituent such as fat.²⁴ It appears from all available observations that, with wide variations in individual infants and in the same infant at different times, the general tendency in neonatal life is for feedings to leave the stomach

relatively slowly and by a combination of functions working somewhat irregularly and unpredictably. And this is quite in keeping with what might be expected of a viscus poorly provided with muscle, and previously in a state of more or less suspended animation from lack of any stimulus to function. Of significance is the fact that no relationship seems to exist between the rapidity of digestive motor activities and the general state of health or gain in weight of the subject. The conclusion seems justified that gastric digestion (or digestive preparation) is not a factor of primary importance to nutrition at this time of life.

Gastric movements of another sort not visualized by barium studies are of some interest in this general connection. These are the contractions due to hunger, which are, of course, in abeyance after barium is fed. The normal human stomach manifests these movements when it becomes fairly empty, about three hours after a meal. Their presence can be discovered only by placing a balloon in the stomach, inflating it a little, and connecting its orifice with a recording device—a technique which has been satisfactorily shown to produce no disturbing stimuli of its own. Contractions thus recorded appear in waves of increasing frequency and degree, and are inhibited not only by placing food in the stomach but also merely by placing it in the mouth. Observers have proven that hunger contractions are notable in the stomachs of newborn and, especially, premature infants (age 7 to 36 days) where they begin to appear an hour or more after an ordinary feeding.^{9,25} In full term infants (age 8–12 days) the contractions begin from 2 to 4 hours after eating. Since in either type of subject these waves have been found to come on before the stomach has emptied itself, they do not necessarily mean that the stomach requires more food. Taylor,²⁵ who studied the subject with care, concluded that such “hunger” contractions are not regularly a cause of crying or even waking, in the very young infant. In contrast to the adult behavior, these contractions are not inhibited by any type of food placed in the infant’s mouth until appreciable quantities are swallowed.

Barium studies have shown certain peculiarities of the newborn infant’s small intestine. Although the duodenum often has a roentgenologic appearance similar to that of the adult the jejunum apparently lacks sufficient muscle to throw the outline of its contents into the mucosal folds commonly observed in older subjects. Segmentation into isolated masses occurs in the jejunum as the later portions of food leave the stomach. In the ileum a grouping of the milk into small and separate segments is very characteristic. The appearance is that often called “puddling,” a picture once

thought to be pathognomonic of celiac disease²⁶ or of deficiency in intake of some constituent of the vitamin B group. There is some difference of opinion as to whether the clumping or "puddling" of barium roentgenologically observable in these situations is due to intestinal hypermotility^{9,27} or to the opposite condition of hypomotility. It is interesting that in celiac disease, this picture is abolished by the administration of mecholyl (acetyl-beta-methylcholine chloride) which is known to increase intestinal tone, peristalsis, and segmentation.²⁸ For this reason and because of the general status of intestinal muscle in neonatal life, it is probable that the phenomena revealed by barium examination at that age are assignable to the same generally deficient tonus which seems to characterize the stomach as well.

The food of most newborn infants enters the cecum three to six hours after the meal, though this of course does not mean that the entire amount fed arrives there so soon. By contrast, the colon is somewhat more active in the newborn infant than it is in later life; some of the food seems to reach the descending colon about two hours after the meal gets to the cecum, and within 24 hours after the ingestion of food, evacuation of the corresponding feces appears to be almost or entirely completed in most newborn infants. Colonic muscular activity is such that only 60 per cent of one series of infants aged less than ten days, in whom barium enemata were used for study, retained sufficient barium for a long enough time to allow the making of satisfactory roentgenograms.¹⁷ The colon tends to be somewhat redundant and to present vagaries in positions; its haustrations are relatively shallow, and it appears roentgenologically to be completely filled by only 60 to 75 cc. of the opaque mixture.¹⁹

In the adult, food begins to enter the cecum about $2\frac{1}{2}$ hours after it reaches the stomach, while the first part of the meal appears in the stool about 24 hours after eating. But in the newborn infant the cecum is not reached by any of the food until from three to six hours after its ingestion, whereas it appears in the stool in only a little more than eight hours, most of the non-absorbed portion usually being excreted within 24 hours. Kahn²⁹ found by means of dyes that some portions of feedings could be identified in the stool about 15 hours after eating, while in several premature infants aged between two days and five months the time was definitely shortened to about 10 hours. In prematures there was less variation in the interval than in babies born at full term. The assumption is that in the premature the rapidity of passage through the large

bowel must be even more marked than is the same process in the "mature" infant.

To sum up the digestive mechanics of newborn life, it may be said that part of the alimentary content passes rather quickly through each portion of the tract but, on the other hand, a certain amount tends to lag unduly. This takes place especially in the stomach and upper bowel, less in the lower ileum, and not at all in the colon. Much of this characteristic performance is due probably to a paucity of musculature and perhaps to a disorganization of nerve impulses and effects. Finally, the presence of swallowed air is especially noteworthy in newborn and very young subjects.

Soveri's most careful study³⁰ of air ingestion did not, unfortunately, include many infants in the immediately post-natal period but the newborn is different only in degree from the slightly older baby. Reasoning from this author's work it may be stated that air tends to disappear from the stomach fairly rapidly, passing (with the earlier portions of the meal) into the intestine in about thirty minutes. Thereafter its progress is rather slow, for it is moved along or absorbed much less efficiently than in the older subject. Paine and Nessa³¹ found that in newborn life and indeed until about a year of age, air is more or less equally distributed between the small and large bowels; after that time the presence of air other than transiently in the small bowel becomes increasingly uncommon. It is of interest that air begins to accumulate in the stomach surprisingly soon after the normal infant's birth, so that films taken within five minutes often show a gastric bubble. This usually has been passed well along into the ileum within the first two hours of life,³¹ so quickly and so regularly does this occur that evidences of interference with the passage are of much usefulness in the diagnosis of obstructive conditions in newborn patients.

THE FETAL AND NEONATAL DIGESTIVE SECRETIONS

The embryologist, Needham, who has given the best review³² of the role and development of enzymes in pre-natal life is not very happy over the accuracy of available knowledge about these matters. Having tabulated the results of researches (up to 1931) he makes the rather pointed statement that "the main bulk of the large literature on this subject [enzymes in mammalian embryos] has been the work of medical investigators in obstetrical clinics, using as often as not very questionable methods, and there is, therefore, little need to go minutely into the tables." In an introduction to the same chapter is an illuminating passage which deserves

quoting for the light it throws on the whole question of the origin of digestive secretions in the body: "A good deal of the work which must be mentioned in this section seems to have been inspired by the idea that, if one could get hold of the original egg-cell, no enzymes would be found to be present at all, and that they all arise, one after the other, in a kind of ontogenetic procession from an ovum completely innocent of any. This idea has only to be stated for its absurdity to be recognized, and it is far more probable that no living cell can exist without at least a protease, a lipase, and an amylase (and, of course, many oxidizing enzymes). . . . In any case, it seems likely that the embryonic body starts life with an assortment of fundamental enzymes, or a collection of fundamentally active surfaces, to which, as development goes on, certain others are added, and from which possibly some are subtracted."

This conception removes much of the mystery (though not the fundamental one) as to the origin of these active principles in the infant's body, and makes it necessary only to state what is known as to the fetal age at which they can first be demonstrated with certainty. In the case of the stomach, the glands of which develop in the fourth and fifth months of embryonic life,^{33,34} the presence of hydrochloric acid,³⁵ pepsin,³⁶ and rennin,³⁵ may be demonstrated from this period and consistently thereafter. Beside these a gastric lipase has been found equally early by some, though denied by others. Certainly all secretions thus far mentioned, together with some amylase, are supplied by the stomach at the time of birth. Enzymes have been demonstrated in the duodenum and intestine in the fourth fetal month,³⁶⁻³⁸ and though the sequence of their specific appearance has not been firmly established their presence at birth is generally accepted. The pancreatic lipase and trypsinogen are probably present in the fourth month³⁹ and after the fifth there seems to be no doubt about any pancreatic ferment except amylase. This substance may appear at birth, but Keene and Hewer³⁸ did not find it consistently then; the question of its post-natal secretion is discussed below. In a few premature infants ($3\frac{1}{4}$ to $4\frac{1}{4}$ pounds) no amylase was found in the duodenal contents at three weeks although the other pancreatic ferments appeared with almost unimpaired strength. Ptyalin is, however, present in the saliva through the last half of gestational life^{36,37} and disaccharide-splitting enzymes are available in the intestine for some time before birth.

In the newborn human infant, investigation has been directed especially toward the amount of hydrochloric acid secreted by the stomach. That such a secretion is usually present in premature

infants is shown by most examinations,^{35,40-42} and only one observer⁴³ is in disagreement with this conclusion. Below what exact weight or chronological age no free hydrochloric acid is to be expected in viable prematures has not been settled. A wide normal range is possible, as Miller showed in a study of the fasting gastric juice in infants less than eight hours after birth.⁴² In his subjects weighing less than 5 pounds, the average amount of free acid was about 12 cc. (of N/10 HCl per 100 cc. gastric juice), although in the calculation of this average were included a majority of infants who actually had fasting achlorhydria. The latitude of findings appears in Figure 26, reprinted from his work. In this it will be observed that similar examinations of full-term infants revealed an average of about 27 cc. free acid. Less than 10 per cent of the total group of "mature" infants were achlorhydric. Miller considered that these newborn infants of full gestation showed about the same levels of free hydrochloric acid as would be expected in the stomach of the average adult. This rather surprising degree of acid production so soon after full-term birth and before any stimulus of food in the stomach is almost uniformly revealed by the observations of others. Tangl,⁴⁴ Hess,⁴⁵ Griswold and Shohl,⁴⁶ and Ritter⁴⁷ are among those who have recorded it, either in units of N/10 HCl or in pH measurements which range in most studies from about 1.3 to 4.6 for representative groups of infants. The amount of acidity seems to be roughly related to the gross amount of gastric juice secreted; usually more juice can be withdrawn from those infants in whom the reaction is most acid.⁴² The amount of secretion present soon after birth is sometimes surprising. Taylor²⁵ recovered 6 cc. (with a free acid of 50) from an infant aged two hours, and in the experience of Hess,⁴⁵ 10 cc. of gastric juice were sometimes obtained. The average amount present in the first hours of life is 4 or 5 cc.

A second fact of interest is that the gastric acidity is higher on the first day of life than later in the newborn period. Though this has not been the case in all measurements of hydrogen ion concentration⁴⁶ it appears clearly in Miller's very detailed study of the free and total gastric acidity in a large series of infants.⁴² The average free acid of 17.2 cc. (N/10 HCl/100 cc. juice) on the first day fell to none by the eighth day, with free acid reappearing towards the end of the second week, and then rising to an average of only 2 cc. in the fourth. The course and range of total gastric acidity is nicely shown in Miller's diagram (Figure 27). The same general recession of acidity after the first few neonatal days appears when the response of the stomach to histamine is tested.⁴⁸

Why the generally low level of gastric acidity during infancy

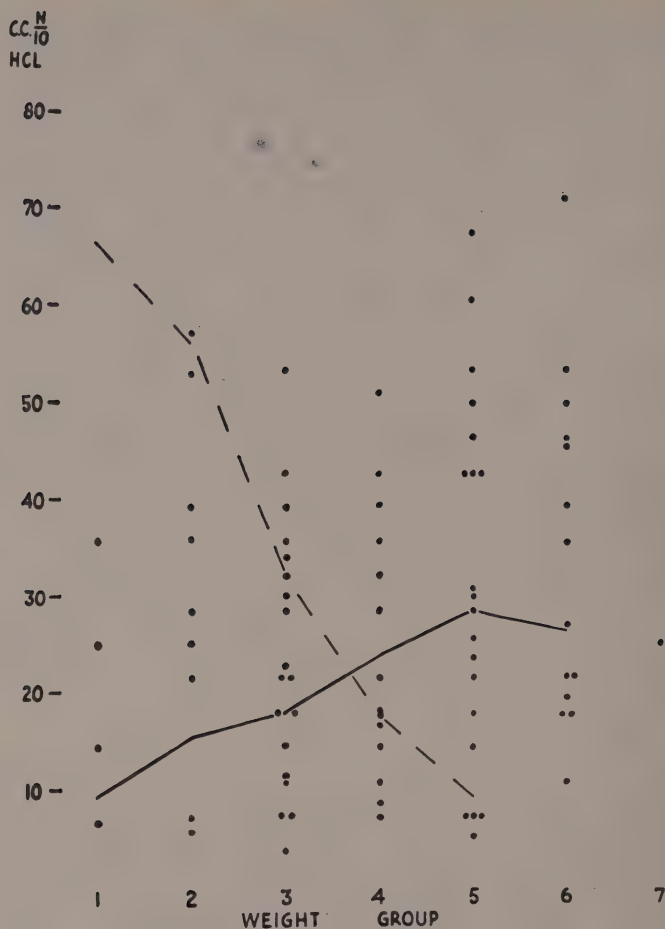


FIGURE 26

Gastric acidity (free) of premature and full-term infants within 8 hours after birth. The dots, each of which represents one infant, indicate the range of findings. The solid line represents the average acidity in each of the following weight groups:

Group	Number of Cases
1. Under $4\frac{1}{2}$ lb.	9
2. $4\frac{1}{2}$ –5 lb.	16
3. 5 – $5\frac{1}{2}$ lb.	24
4. $5\frac{1}{2}$ – $6\frac{1}{2}$ lb.	17
5. $6\frac{1}{2}$ – $7\frac{1}{2}$ lb.	22
6. Over $7\frac{1}{2}$ lb.	18
7. Average adult	

The interrupted line represents the percentage of infants showing achlorhydria encountered in each group. (Miller, *Arch. Dis. Child.*, 16: 22, 1941.)

should be preceded by this immediately postnatal excess of secretion has been the subject of some theorizing. Apparently it cannot be explained as a reflection of the general status of acid-base balance in body fluids. Sendroy⁴⁹ quotes work which showed that

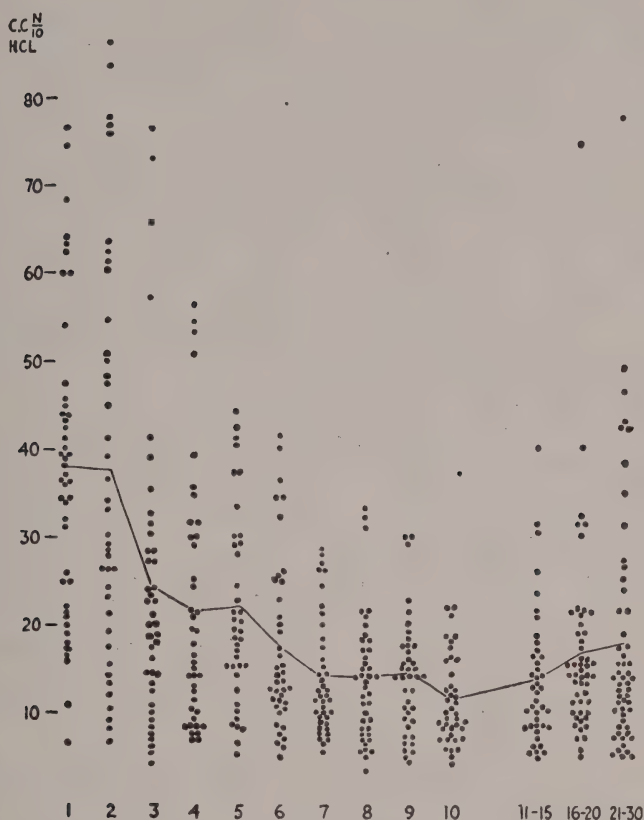


FIGURE 27

Total acidity of gastric juice during the first month of life. Dots represent individual determinations, line indicates their averages. (Miller, *Arch. Dis. Child.*, 16: 22, 1941.)

"neither oral ammonium chloride acidosis in man nor extreme sodium bicarbonate alkalosis in dogs was found to have any effect on gastric acidity. In spite of previous contrary evidence, the gastrointestinal tract is therefore regarded . . . as a stable receptor in which deviations are produced only by profound changes." Nor is there indeed any unanimity of evidence that the normal infant's blood is "acidotic" in its pH values nor elevated in chloride content

during the time of high gastric acidity.⁵⁰ Indeed if there does occur a metabolic acidosis with accumulation of chloride⁵¹ this tends to appear on the third day, when gastric hydrochloric acid levels have definitely fallen. Gilman and Cowgill⁵² have shown that dehydration, experimentally produced in the animal, is accompanied by an increase in gastric acidity, but again the dehydration of the infant tends to be increasing just when the gastric acidity is on the wane. A recent review by Friedman⁵³ touches upon other theories. The most plausible is that a gastric secretory stimulant from the mother's blood may mingle with the fetal blood until the act of birth severs the connection between the two organisms. If such a circulating hormonal substance (gastrin) is present, it might well be stored in the fetus to some extent but dissipated soon after birth and unable to stimulate the newborn infant's gastric secretion quantitatively or qualitatively thereafter. That the stomachs of newborn animals are responsive to gastrin parenterally introduced has been demonstrated.⁵⁴ Whether the general mechanism involved could play any part in the rate of hematopoietic activity before and after birth is an interesting subject of conjecture.

In any case, for the immediately practical matter of digestion during the first two weeks of life there seems to be sufficient hydrochloric acid present for the partial activation of pepsin. The optimum pH for peptic digestion of protein is stated to be 2.0²⁴ but considerable activity can occur at pH 4.0, and although the infant's stomach may be at first more acid and later less so than this level, some digestion of milk protein is certainly possible. In passing, it may be noted that whatever germicidal action may be expected from gastric acidity must be at its most potent level during the time of bacterial invasion soon after birth.

So much less attention has been devoted to the other digestive substances in the newborn stomach that only a brief statement can be made concerning pepsin and rennin. The glands secreting them are present at birth and well before⁵⁵ and the substances are measurable neonatally, though in perhaps lower concentrations than in later infancy.^{22, 56-58} The effective acidity at which rennin clots milk is between pH 6 and 6.5, so that in the circumstances of newborn life, rennin probably has little opportunity to function. That even the fairly high protein content of colostrum and early milk is dealt with quite well by the available digestive secretions will be shown in a later section. A certain amount of fat may be split by the gastric lipase which has been found present in the newborn period, and perhaps the total gastric acidity may result in some part from the fatty acids thus formed in the stomach.^{59, 60}

Unlike the stomach and duodenum, the intestine of the child at birth has a certain content of material, the meconium, which contains substances and gives reactions that allow certain deductions as to fetal life processes. Meconium is first demonstrable in the bowel of the human fetus at four or five months' gestation.² Because a certain amount of liquid is absorbed from the intestine while the fetal environmental material continues to be swallowed, meconium tends to become increasingly firm, solid, and dark, as gestational life progresses. At birth its amount is variously estimated as from 60 to as much as 200 grams,⁶¹ and its physical characteristics include a viscid, sticky consistency and a dark greenish-brown to black color. It has been subjected to considerable microscopic and chemical study⁶² with somewhat conflicting results, but there is agreement as to its slightly acid reaction^{63,64} and its varied composition of cells from the upper alimentary tract, mouth, and skin, fatty material from the vernix caseosa, and hairs shed from the lanugo. The various enzymes which are secreted in late fetal life are also present together with calcium soaps and cholesterol crystals and sufficient bilirubin and biliverdin to contribute most of the characteristic color. Occult blood is not an abnormal constituent, but whether its source is ingested maternal blood or the blood of the fetus itself is not known. Meconium may first be evacuated (under abnormal circumstances) *in utero*; usually the normal infant passes some of it within the first ten hours⁶⁴ and meconial characteristics disappear from the fecal mass by about the fourth day after birth.

Digestion and absorption in the neonatal intestine are probably facilitated by the presence of a highly developed intestinal mucosa, the elements of which compare favorably with those of the same region in the adult.⁵⁵ Moreover, there is evidence that the infant has glands of the Lieberkuhn type scattered among the ordinary mucous glands of the colon, where no such secretory structures appear in adult life.⁵⁵ Whatever be the time-table of their fetal appearance, no substantiated evidence has been brought forward indicating any critical lack of protein-, sugar-, or fat-splitting ferments in the intestinal juices at birth, even when the infant is born a month or more prematurely.⁶⁵ Nor is there anything (except inference based upon beliefs concerning icterus neonatorum) to indicate that the digestive functions of the liver are seriously at fault in neonatal life. As to the part played by the pancreatic enzymes, duodenal analyses have shown that pancreatic amylase and, perhaps, lipase are not very actively formed in the first few weeks after birth. Although Ibrahim⁶⁶ reports the pancreas to contain amy-

lolytic ferment at birth, the data of Klumpp and Neale⁶⁷ indicate that the amounts recoverable in duodenal juice are comparatively meager even through the first twelve months of life, and a relative absence of this substance appears from other studies such as those portrayed graphically in the accompanying chart from Farber's laboratory.⁶⁸ A deficiency of lipase is less marked but nevertheless present⁶⁷ for about three months. How much starch digestion is actually available from the ptyalin of the saliva is not certain. Al-

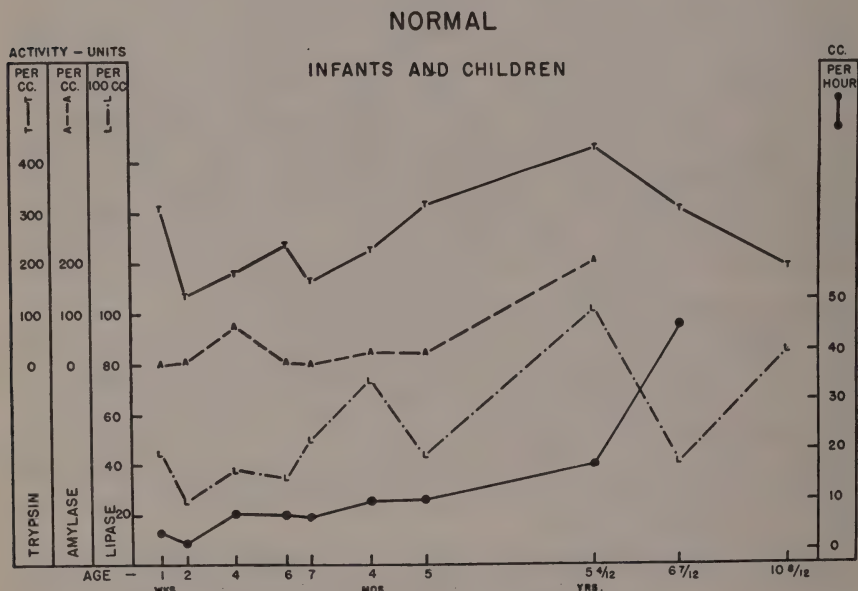


FIGURE 28

Relationship between age and the digestive activity and quantity of pancreatic enzymes. (Courtesy of Dr. Sidney Farber.)

though it is a time-honored dictum that ingested polysaccharides are wasted by the digestive tract before the third or fourth month of life, the only clinical investigation upon this point⁶⁹ does not entirely substantiate this belief, as is pointed out in a later section.

Something may be said here of the origin and nature of the bacteria which, though absent from the alimentary tract of the fetus and of the infant at birth, normally make their appearance in the feces within a few hours thereafter. Since, in the adult about one-half of the daily fecal mass is composed of micro-organisms, the original invasion of these alimentary inhabitants, which are never again absent, has been a matter of some interest to bacteriologists. Their prompt advent is a striking example of the principle that the

alimentary tube is really not within the actual interior of the body. For a review of the more strictly bacteriological aspects of the subject the reader is referred to the papers of Salomon⁷⁰ and of Hall and O'Toole,⁷¹ and it will be sufficient to indicate here what general types of organisms take up their existence in the gastrointestinal tract, by what routes they arrive, and at what times. The commonest species which may be cultured in early passages of meconium are usually various micrococci allied to and including the *m. albus*, as well as the *streptococcus fecalis* and *mitis* (sometimes hemolyticus⁷⁰), the colon bacillus, and two forms of lactobacilli. As the meconium becomes supplanted with an intestinal content derived from milk, these are more or less overshadowed by the *bacillus bifidus*, and, in the upper intestinal region, the *streptococcus enteritidis* (*m. ovalis*, Bargaen's bacillus⁷²).

Hall and O'Toole⁶⁴ found the first discharges of meconium, usually passed by the tenth hour after birth, to contain culturable organisms in about 40 per cent of a series of 50 infants. When specimens were passed in the first five hours 87 per cent of those investigated were sterile, but by the end of the first 24 hours the meconium of all 50 infants was found to be infected. The source of organisms reaching the gastrointestinal tract appears to be the mouth, as might be expected, although some retrograde invasion of the rectum has been shown to occur also. The vaginal flora of the mother are usually found to be the microorganisms which enter the body in this manner.⁷⁰ Bacteria of 12 different species which could be traced to the maternal vagina, the skin of the mother's breast, and other objects brought in contact with the baby's face, were found in the mouths of 19 infants during the first 24 hours of life. The specific organisms identified in the mouth appeared in the stools a few hours thereafter—an indication that even the high gastric acidity of immediate postnatal life is far from being reliably germicidal. Infants fed artificially may acquire the initial bacterial flora of the nose and throat by direct contact with adult attendants. Bacteria are carried upon droplets of saliva, and may thus reach the baby even though masks are worn by nursing personnel.⁷³

It is natural that those authors who have been most interested in the neonatal intestinal flora have from time to time suggested that the so-called "transitional stools"—greenish, often slimy, and far from homogeneous feces, which usually appear after the meconium and before the normal light yellow, pasty stools of the normal infant—are in some part the result of local irritation from the normal bacterial invasion. Since no one has yet observed a baby whose intestinal tract has been kept germ-free during the first week of life, this remains in the realm of theory.

CLINICAL SUMMARY

The gastrointestinal tract of the newborn infant shows a greater development of secretory and absorbing surfaces than of supporting musculature. This makes for easy absorption of food but also for distension, for alterations in visceral topography, and for certain peculiarities of peristaltic motility. Barium studies have shown a marked variation of gastric size in accordance with the amount of food and air swallowed so that the normal capacity of the stomach, although of little importance, is much greater than measurements of anatomical specimens indicate. By contrast with the adult, the gradient of muscle movement is slow in the upper alimentary tract but gains speed in the lower portions. Although gastric emptying time allows the larger portion of a feeding to leave the stomach in two hours, some may remain for eight hours or more. In premature infants the process may be somewhat more rapid, but in the full-term baby there are no characteristic variations associated with the state of general health or of weight gain, and it is probable that ordinary alterations in amount of fat, protein, or carbohydrate in the diet exert no special influence.

Roentgenological examinations show a normal tendency for clumping of barium in the upper bowel with patterns usually considered significant of deficient muscle tone. The major portion of a feeding reaches the cecum in six hours, and the fecal residue begins to be passed within 15 hours after ingestion. In premature infants the process takes a shorter time. Air swallowing, which begins with extra-uterine life, contributes a variable amount to gastrointestinal distension, and is accompanied by a characteristic neonatal distribution of air quite generally through the bowel.

An adequate group of enzymes for all simple foods except starches appears to be available even before premature birth, though pancreatic amylase remains deficient for some months of early infancy. The output of hydrochloric acid in the stomach is strikingly high for a short period immediately after birth, so as to suggest the effect of placentally transmitted secretory hormone from the mother's blood. None of the other digestive juices displays a similar post-natal excess.

Enzymes, residue from swallowed amniotic fluid, desquamated cells from the mucosa, and traces of blood from unrecognized sources, largely compose the meconium, of which 60 to 200 grams are present in the bowel at birth though smaller amounts are found much earlier in fetal life. Some meconium is passed within the first 10 hours postnatally; all of it has usually been evacuated by the fourth day. The meconium, and the alimentary tract in general, is

sterile at birth but often contain bacteria five hours later, and after 24 hours have passed always does so. These largely arrive by ingestion, though retrograde contamination through the rectum is possible. No proof is available that the mildly disturbed "transitional" stools appearing after the meconium may be due to this invasion.

In general, the normal newborn patient has a physical capacity for food which is unlikely to be exceeded by any ordinary dietary program. The enzymes available for digestion have not been found inadequate to deal with any type of food except complex carbohydrates. The actual assimilation of foods after digestion is discussed in the next chapter.

BIBLIOGRAPHY

1. FABER, H. K.: Food requirements in newborn infants; a study of the spontaneous intake, *Am. J. Dis. Child.* 24: 56, 1922.
2. WINDLE, W. F.: *Physiology of the Fetus: Origin and Extent of Function in Prenatal Life*, Philadelphia, W. B. Saunders Company, 1940.
3. ZUNTZ, N.: Ueber die Quelle und Bedeutung des Fruchtwassers, *Arch. f. d. ges. Physiol.* 16: 548, 1878.
4. WISŁOCKI, G. B.: Contributions to Embryology 11: 47, 1920.
5. DE SNOO, K.: Das trinkende Kind im Uterus, *Monatsschr. f. Geburtsh. u. Gynäk.* 105: 88, 1937.
6. EHRHARDT, K.: Atmet das Kind in Mutterleib? (Eine röntgenologische Studie), *München. Med. Wehnschr.* 86: 915, 1939.
7. HENDERSON, S. G.: The gastrointestinal tract in the healthy newborn infant, *Am. J. Roentgenol.* 48: 302, 1942.
8. BECKER, R. F., WINDLE, W. F., BARTH, E. E., and SCHULZ, M. D.: Fetal swallowing, gastro-intestinal activity and defecation in amnio; an experimental roentgenological study in the guinea pig, *Surg., Gynec. and Obst.* 70: 603, 1940.
9. CARLSON, A. J., and GINSBURG, H.: The tonus and hunger contractions of the stomach of the new-born, *Am. J. Physiol.* 38: 29, 1915.
10. BENEKE: Ueber die Länge des Darmkanals bei Kindern, sowie über die Capacität des Magens Neugeborener, *Deutsche Med. Wehnschr.* 6: 433, 448, 1880.
11. SCAMMON, R. E.: A Summary of the Anatomy of the Infant and Child, in *Pediatrics* (Vol. 1), edited by I. A. Abt. Philadelphia, W. B. Saunders Company, 1923.
12. GUNDOBIN, N.: Ueber den Bau des Darmkanals bei Kindern, *Jahrb. f. Kinderh.* 33: 439, 1892.
13. PISEK, G. R., and LEWALD, L. T.: The anatomy and physiology of the infant stomach; serial roentgenograms, *Am. J. Dis. Child.* 6: 232, 1913.
14. VOGT, E.: Fortsetzung der Röntgenuntersuchungen der inneren Organe des Neugeborenen, *Fortschr. a. d. geb. d. Röntgenstrahlen* 29: 405, 1922.
15. ROGATZ, JULIUS: Röntgenologische Studien über die peristaltische Funktion des Magens im Säuglingsalter und ihre Bedeutung für die Entstehung des habituellen Erbrechens, *Ztschr. f. Kinderh.* 38: 1, 1924.

16. DeBACKER, and VAN DE PUTTE: Digestive transit in normal sucklings, *Am. J. Roentgenol. & Rad. Ther.* 14: 363, 1925.
17. BOUSLOG, J. S., CUNNINGHAM, T. D., and others: Roentgenologic studies of the infant's gastrointestinal tract, *J. Pediat.* 6: 234, 1935.
18. GOLDEN, R.: Abnormalities of the small intestine in nutritional disturbances; some observations on their physiologic basis, *Radiology* 36: 262, 1941.
19. HENDERSON, S. G., and BRIANT, W. W., JR.: The colon in the healthy newborn infant, *Radiology* 39: 261, 1942.
20. THEILE, P.: Zur Radiologie des Säuglingsmagens (Mit besonderer Berücksichtigung der Gestalts- und Lageveränderungen dieses Organes bei der Füllung und Entleerung), *Ztschr. f. Kinderh.* 15: 152, 1917.
21. VOGT, E.: Röntgenuntersuchungen über die Respirations-, Zirkulations- und Digestionsorgane Neugeborener, *Arch. f. Gynäk.* 107: 15, 1917.
22. LEO, H.: Ueber die Function des normalen und Kranken Magens und die therapeutischen Erfolge der Magenausspülung in Säuglingsalter, *Berl. Klin. Wehnschr.* 25: 929, 1888.
23. FREUDENBERG, E., and WITTICH, H.: Untersuchungen zur Verdauungsphysiologie des Säuglings; Jejunalsondierung, *Ztschr. f. Kinderh.* 52: 696, 1932.
24. IVY, A. C.: *Physiology of the Gastro-intestinal Tract*, Vol. 1, *Practice of Pediatrics*, Edited by Joseph Brennemann, Hagerstown, W. F. Prior Company, 1942.
25. TAYLOR, R.: Hunger in the infant, *Am. J. Dis. Child.* 14: 233, 1917.
26. ZWERLING, H., and NELSON, W. E.: Roentgenologic pattern of the small intestine in infants and children, *Radiology* 40: 277, 1943.
27. CRANDALL, L. A., JR., CHESLEY, F. F., HANSEN, D., and DUNBAR, J.: Relationship of P-P factor to gastrointestinal motility, *Proc. Soc. Exper. Biol. & Med.* 41: 472, 1939.
28. MAY, C. D., MCCREARY, J. F., and BLACKFAN, K. D.: Notes concerning the cause and treatment of celiac disease, *J. Pediat.* 21: 289, 1942.
29. KAHN, WALTHER: Weitere Mitteilungen über die Dauer der Darmpassage im Säuglingsalter, *Ztschr. f. Kinderh.* 33: 48, 1922.
30. SOVERI, V.: Der Verlauf der Luft durch den Verdauungskanal des Säuglings, *Acta paediat. (Supp. 3)*, 23: 1, 1939.
31. PAINE, J. R., and NESSA, C. B.: Observations on the distribution and transport of gas in the gastrointestinal tract of infants and young children, *Surgery* 11: 281, 1942.
32. NEEDHAM, J.: *Chemical Embryology*, Vol. 3, New York, The Macmillan Company, 1931.
33. KOLLIKER, ALBERT: *Entwicklungsgeschichte des Menschen und der höheren Thiere*, Leipzig, Wilhelm Engelmann, 1879.
34. SCOTT, G. H.: Growth of crypts and glands of the human stomach, *Am. J. Dis. Child.* 30: 147, 1925.
35. DUDIN, H.: *Inaug. Diss.* Leningrad, 1904.
36. IBRAHIM, J.: Trypsinogen und Enterokinase beim menschlichen Neugeborenen und Embryo, *Biochem. Ztschr.* 22: 24, 1909.
37. WOODMAN, J., HEWER, E. E., and KEENE, M. F. L.: Communication to the Physiological Society, November, 1926; cited by Needham, Ref. 32 above.
38. KEENE, M. F. L., and HEWER, E. E.: Digestive enzymes of human foetus, *Lancet* 1: 767, 1929.

39. TACHIBANA, T.: Physiological investigation of the fetus; trypsinogen in pancreas, *Jap. J. Obst. & Gynec.* 10: 27, 1927, and Lipase in pancreas, *Idem.* 11: 92, 1928.
40. POLLITZER, R.: La secrezione gastrica nel neonato ancora digiuno, *La Pediatria* 29: 253, 1921.
41. VON MORITZ, D., and SCHMITT, A.: Magenfunktionsprüfung bei Frühgeborenen, *Arch. f. Kinderh.* 99: 23, 1933.
42. MILLER, R. A.: Observations on the gastric acidity during the first month of life, *Arch. Dis. Childhood* 16: 22, 1941.
43. GALEOTTI FLORI, A.: Ricerche sulla secrezione gastro-duodenale negli immaturi, *Riv. di. clin. pediat.* 38: 193, 1940.
44. TANG, FRANZ: Untersuchungen über die Hydrogenionenkonzentration im Inhalte des nüchternen menschlichen Magens, *Arch. f. d. ges. Physiol.* 115: 64, 1906.
45. HESS, A. F.: The gastric secretion of infants at birth, *Am. J. Dis. Child.* 6: 264, 1913.
46. GRISWOLD, C., and SHOHL, A. T.: Gastric digestion in new-born infants, *Am. J. Dis. Child.* 30: 541, 1925.
47. RITTER, J. A.: Fractional gastric analysis in the newborn; preliminary report, *Pennsylvania M. J.* 44: 1321, 1941.
48. CUTTER, R. D.: Normal gastric secretion of infants and small children following stimulation with histamine, *J. Pediat.* 12: 1, 1938.
49. SENDROY, J., JR.: Acid-Base Metabolism, *Annual Review of Biochemistry* VII, 1938.
50. HOAG, L. A., and KISER, W. H., JR.: Acid-base equilibrium of newborn infants; I. Normal standards, *Am. J. Dis. Child.* 41: 1054, 1931.
51. MARPLES, E., and LIPPARD, V. W.: Acid-base balance of new-born infants; II. Consideration of the low alkaline reserve of normal new-born infants, *Am. J. Dis. Child.* 44: 31, 1932.
52. GILMAN, A., and COWGILL, G. R.: Osmotic relations of blood and glandular secretions; regulatory action of total blood electrolytes on concentration of gastric chlorides, *Am. J. Physiol.* 99: 172, 1931.
53. FRIEDMAN, M. F. H.: Gastric secretion in the newborn, *Am. J. Digest. Dis.* 9: 275, 1942.
54. SUTHERLAND, G. F.: Physiology of stomach; response of gastric gland to secretin before and shortly after birth, *Am. J. Physiol.* 55: 398, 1921.
55. BLOCH, C. E.: Anatomische Untersuchungen über den Magen-Darmkanal des Säuglings, *Jahrb. f. Kinderh.* 58: 121, 1903.
56. SZYDLOWSKI, ZDZISLAUS: Beitrag zur Kenntniss des Labenzym nach Beobachtungen an Säuglingen, *Jahrb. f. Kinderh.* 34: 411, 1892.
57. HAMBURGER, F., and SPERK, B.: Untersuchungen über die Magenverdauung bei Neugeborenen Brustkindern, *Jahrb. f. Kinderh.* 62: 495, 1905.
58. REEVE-RAMSEY, WALTER: Über das Vorhandensein von Pepsin im Magen des Säuglings und die Abhängigkeit seiner verdauenden Kraft von der Anwesenheit von Salzsäure, *Jahrb. f. Kinderh.* 68: 191, 1908.
59. SEDGWICK, J. P.: Die Fettspaltung im Magen des Säuglings, *Jahrb. f. Kinderh.* 64: 194, 1906.
60. IBRAHIM, J., and KOPEC, T.: Die Magenlipase beim menschlichen Neugeborenen und Embryo, *Ztschr. f. Biol.* 53: 201, 1909.
61. GRULEE, C. G., and BONAR, B. E.: The Newborn; Physiology and

- Care, New York, D. Appleton & Company, 1926.
62. VON REUSS, A. R.: *The Diseases of the Newborn*, London, John Bale, Sons & Danielsson, 1921.
 63. NORTON, R. C., and SHOHL, A. T.: The hydrogen ion concentration of the stools of new-born infants, *Am. J. Dis. Child.* 32: 183, 1926.
 64. HALL, I. C., and O'TOOLE, E.: Bacterial flora of first specimens of meconium passed by 50 new-born infants, *Am. J. Dis. Child.* 47: 1279, 1934.
 65. LEVINE, S. Z., and GORDON, H. H.: Physiologic handicaps of the premature infant; their pathogenesis, *Am. J. Dis. Child.* 64: 274, 1942.
 66. IBRAHIM, J.: Neuere Forschungen über die Verdauungsphysiologie des Säuglingsalters, *Versamml. Gesellsch. Deutscher Naturf. u. Aerzte* 80: 316, 1908.
 67. KLUMPP, T. G., and NEALE, A. V.: Gastric and duodenal contents of normal infants and children; duodenal enzyme activity and gastric and duodenal reactions, *Am. J. Dis. Child.* 40: 1215, 1930.
 68. FARBER, S., MADDOCK, C. L., and SHWACHMANN, H., Unpublished data.
 69. BENTIVOGLIO, G. C.: Nuovi criteri clinici intorno al comportamento digestivo e all'uso delle sostanze amidacee nei primi mesi di vita, *Riv. di clin. pediat.* 26: 96, 1928.
 70. SALOMON, RUDOLPH: Beiträge zur Entstehung der Mund- und Rektumkeime beim Neugeborenen, *Zentralb. f. Gynäk.* 46: 563, 1922.
 71. HALL, I. C., and O'TOOLE, E.: Intestinal flora in new-born infants, with description of a new pathogenic anaerobe, *Bacillus difficilis*, *Am. J. Dis. Child.* 49, 1935.
 72. KENDALL, A. L.: *Bacteriology of the Gastro-intestinal Tract*, in Vol. I, *Practice of Pediatrics*, Edited by Joseph Brennemann, Hagerstown, W. F. Prior Company, 1942.
 73. TORREY, J. C., and REESE, M. K.: Initial aerobic flora of newborn (premature) infants, *Am. J. Dis. Child.* 67: 89, 1944.

Chapter IX

FETAL AND NEONATAL NUTRITION: ASSIMILATION AND METABOLISM OF SPECIFIC FOOD SUBSTANCES

- Section 1* . . . Proteins, and the Metabolism of Nitrogenous Substances in General
Section 2 . . . Carbohydrate Assimilation and Metabolism
Section 3 . . . Fat Assimilation and Metabolism
Section 4 . . . Clinical Summary
-

PROTEINS, AND THE METABOLISM OF NITROGENOUS SUBSTANCES IN GENERAL

NITROGENOUS SUBSTANCES ENTER the body as protein foods. Once digested and absorbed they exist in many different forms: they are fixed in the essential substance of the tissues; they circulate in the blood either as essential components or en route to their assimilation or excretion; and after passage through the kidney, they manifest themselves in various forms and concentrations in the urine. So numerous and diverse are their appearances in the body that a brief description of the major details may not be amiss for purposes of orientation. Such an account must necessarily be a most incomplete outline of protein metabolism but may help to introduce a discussion of this general aspect of neonatal physiology.

Protein foods are normally broken down by digestion to progressively simpler molecules, the simplest of which, the amino acids, are absorbed through the wall of the small bowel. In the normal adult, absorption of more complex nitrogenous substances than these is usually not supposed to occur. Amino acids are carried from the bowel to the liver in the portal circulation, and their increased presence in the blood stream after a protein meal can be shown quantitatively. Amino acid molecules not immediately utilized for constructing protein tissues in the body are broken up (mostly in the liver) and their non-nitrogenous residue burned for energy, stored as glycogen, or transformed into fat. The nitrogenous portion is ultimately formed into urea (the amount of which thus becomes a rough index of protein intake) and then removed from the body by the kidneys. The urea of the blood is the largest single element of the non-protein nitrogenous substances, which also include the amino acids, ammonia, uric acid, creatine, creatinine, and a residue of other substances, the so-called undetermined nitrogen.

The largest share of the non-protein nitrogen in the blood is thus subject to

excretion in the urine. As urea forms most of the blood nitrogen, so it contributes some 80 per cent of the total urinary nitrogen, the balance being largely composed of ammonia (which is conveyed in the urine in accordance with the acid-base equilibrium of the body), creatinine, uric acid, and undetermined residual or "rest" nitrogen. Amino acids are not normally present in the urine except by a process aptly described by Peters and Van Slyke³⁹ as "leakage" through the kidneys. Since undetermined nitrogen is mainly attached to the cells of the blood, its contribution to urine nitrogen is small.

Creatine is not normally present in the urine of adults, but for some unsettled reason does occur in the urine of infants and children. Creatinine, to which creatine is normally converted in the body, appears in the urine at all ages and in a narrowly regulated amount for any individual. The concentrations of creatine and creatinine in the tissues and in the urine of adults are not dependent upon the diet and are thus elements of endogenous (largely muscle) metabolism. Uric acid is formed from the purines of the food and of the body tissues themselves, so that it has both exogenous and endogenous origins. It is supposed that roughly half of the uric acid formed in the body is normally destroyed by the liver and not presented for urinary excretion. Since muscle tissue is high in purine substances, the eating of meats or the metabolism of body muscle during exercise increases the amount of uric acid in the blood; although not increased during pregnancy, Slemons and Bogert¹ found the blood uric acid to be definitely elevated at the time of delivery, especially after prolonged labor. Obviously the levels of urea and of the total non-protein nitrogen in the blood must vary with the rate of protein intake and nitrogen catabolism in the body, as well as in accordance with the excretory efficiency of the kidneys. A relatively small amount of importance is usually attached to the fecal excretion of "endogenous" nitrogen, which is assumed to be not more than 10 per cent of the total ingested.

Separate from the various forms of non-protein nitrogen in the blood are the plasma proteins themselves—the fibrinogen, albumin, and globulin whose functions are in various ways essential to the organism and whose levels are so well defended that only such things as gross disturbances in the diet, in the hydration of the blood, or in the activities of the liver and kidneys cause alterations in their concentrations.

Observations of nitrogen metabolism in the unborn and newborn infant have been somewhat heterogeneous and are, in view of the complexities of nitrogen economy, understandably difficult to correlate. Several measurements have been made of the more important substances in the blood of the mother and her newly born infant, the umbilical vessels serving as the source for the latter samples.²⁻⁵ These have shown a close correspondence not only between the total non-protein nitrogen in the blood of both organisms, the level being about 25–40 mgm. per 100 cc.,³⁻⁵ but also between the concentrations of urea, ammonia, uric acid, and creatinine individually, as though all these substances are able to diffuse without much hindrance across the placenta. The non-protein nitrogen of the fetal blood actually tends to be a trifle higher than that in the maternal blood; moreover the amount in the umbilical

artery blood is greater than that in the umbilical vein⁴ so that the picture of fetal nitrogen excretion *via* the placenta is a clear one. Such a gradient is not quite so regularly demonstrable in the case of uric acid,⁴ possibly because of the formation of this substance in the mother's blood during labor. A more intriguing relationship is that between the amino acid concentrations in the two circulations. Most determinations²⁻⁵ have shown a definitely larger amount of amino acids in blood from the cord than in that simultaneously obtained from the mother, the average values in Naeslund's series being 8.3 and 5.9 mgm. per cent respectively. This can hardly be explained without assigning an active role to the placenta, but, however brought about, it must make for a relatively ample supply of tissue building material to the growing fetus. The averages of one series of figures are given in Table 25.

TABLE 25

AVERAGE CONCENTRATION OF NITROGENOUS SUBSTANCES IN THE BLOOD OF 40 WOMEN AND THEIR NEWBORN INFANTS²

	Maternal Vein	Umbilical Artery	Umbilical Vein
Amino Acid N. mgm. %	6.87	8.19	8.05
N.-P.N. mgm. %	27.25	28.35	27.39
Total protein gm. %	6.55	5.59	5.89
Albumin gm. %	3.73	3.46	3.47
Globulin gm. %	2.82	2.13	2.42

An interesting collection of data was assembled by Lichtenstein⁶ from umbilical cord bloods of premature and mature newborn infants grouped in accordance with their body weights and thus in general with their gestational age. The averages for ten infants in each weight group are presented in the table below:

TABLE 26

RELATIONSHIP BETWEEN MATURITY AT BIRTH AND NITROGENOUS SUBSTANCES IN CORD BLOOD⁶

Birth Weight	N.P.N.	Urea N.	Creatinine	Amino Acid N.	Uric Acid
500-1000 gm.	27.44	11.07	5.05	9.06	2.40
1000-1500 gm.	30.27	13.42	5.19	8.31	3.12
1500-2000 gm.	33.03	13.72	4.96	8.02	3.25
2000-2500 gm.	33.55	14.01	4.86	7.32	3.65
2500-3000 gm.	32.41	13.86	4.33	7.22	3.55
3000 gm. +	35.05	14.93	4.71	6.48	3.70

The increasing amounts of non-protein nitrogen and the similar increases in urea indicate that the developing organism is presumably utilizing a progressively larger amount of nitrogenous food substances and must be presenting an increasing amount of waste to the placenta for excretion. Since the maternal non-protein nitrogen concentration does not increase at all during gestation these changes are not merely passive reflections of alterations in the mother's blood. To what extent increase in uric acid is due to receipt of purines and other precursors from the mother's blood, and how much uric acid (if any) is endogenously formed in the fetal tissues cannot be stated. The steady fall in amino acids from a very high level in the youngest group suggests that these substances are even more generously provided a few months before term than at the time of birth. The figures for creatinine are definitely high but decline toward a more usual level as term approaches. The fact that some of the substances considered increase while others decrease argues against any factor of hydration or dehydration during fetal life as the explanation of these changes.

Considerations of the nitrogen metabolism during gestation are relatively simple as compared with problems of interpretation in the days of adjustment after birth. Following that event the variables of protein digestion and amino acid absorption, and the possibilities of transient tissue protein consumption during the period of post-natal weight loss, all enter any balance sheet of protein economy. The early work of Michel⁷ indicated that on the fourth to eighth days of life the stools contain from 3 to 10 per cent as much nitrogen as was fed in the diet, giving protein "absorption" or "digestibility" co-efficients of between 90 and 97 per cent. From the work of Langstein and Niemann,⁸ and Birk,⁹ impressions of a much more variable and imperfect ability to absorb nitrogen are gained, with absorption of only 70 per cent of the protein in the fourth day's feeding. Such a figure is probably a minimal rather than a true or maximal one.¹⁰ Much depends on the total quantity of nitrogen fed; this obviously allows such latitude that day-to-day comparisons and evaluations of one author's results in terms of another's is almost impossible. Certainly by the end of the second week absorption of nitrogen (which implies digestion of protein) accounts for at least 90 per cent of what is fed. Schloss and Crawford¹¹ have published protocols showing fecal nitrogen* to be as great as 25 to 30 per cent of the dietary nitrogen in the first three days, but to fall to as little as 5 per cent by the seventh day.

*Not all necessarily originating as dietary residue but in some part excreted from the body into the bowel.

In premature infants of a few weeks of age a high absorption of nitrogen has definitely been proven, whether the source of ingested protein be human or cow's milk.^{12,13} Moreover, in the careful studies of Gordon, Levine, and their colleagues,¹² nitrogen continued to be well absorbed even when the protein intake was raised—for short periods—to as much as 9 grams per kilogram of body weight per day. This would clearly indicate a very great digestive capacity for protein by the enzymes of the well-established premature infant, and a ready absorption of the amino acids produced. In fact such amounts of dietary protein would seldom or never be fed in any ordinary diet for a small infant. In general, the evidence indicates that the protein-splitting enzymes and protein absorbing pathways function extremely well as soon as digestion becomes at all established after birth. A somewhat teleological indication of this is furnished by the richness of colostrum in protein.

Granting that digestion and absorption are satisfactorily managed, what can be said of the distribution of nitrogen in the body after these steps have been taken? Amino acids appear in about the same concentration as they attain in the blood of older infants. Hoeffel and Moriarty¹⁴ found the amino acid nitrogen in the blood of five infants aged 9 to 21 days to average about 6 mgm. per hundred cc., a figure slightly above the average they established for 20 normal infants aged less than two years, and indeed high for older children. Other authors¹⁵ have found the value to average about 9.5 mgm. in blood of the first day and 7.9 on the third to fifth days. Apparently during the days of immediate post-natal adjustment when little food is being consumed there is a fairly large amount of tissue-building material in circulation, but whether this occurs because of poor utilization by organs and tissues temporarily disturbed in their functions, or because of some active synthesis in the body, or whether it is only a misleading increase due to hemo-concentration, cannot be stated. Amino acids are present in the urine in abnormally large amounts in the first week^{16,17} but it is also impossible to say that this is "physiological" or that it indicates a transient fault in the function of the kidneys.

The ultimate utilization of the nitrogenous foods is best shown quantitatively by measurements of nitrogen balance. Since the essentials of such studies in any subjects are fairly long test periods (and fore-periods) during which conditions are kept quite constant, it is immediately obvious why so little work has been done during the first few weeks of life when all processes are characteristically unsettled, and why the results are so difficult to evaluate. The interested reader may find critical reviews in Czerney and Keller's

book¹⁸ and in the writings of Pfaundler,¹⁰ who was careful to point out all the sources of technical error. Essentially, the problem is to determine the difference between the nitrogen in the diet and that in the feces, and from this value (representing the protein which has entered the body), to subtract that which leaves in the urine.

TABLE 27
NITROGEN BALANCES OF TWO NEWBORN INFANTS⁹

Infant #1	Nitrogen (gm.)				*Coefficient of Absorption or Digestibility	**Retention Coefficient
	In Diet	In Urine	In Stools	Retained		
1		70	Meconium			
2	418.5	336	Meconium			
3	584.7	392	Meconium			
4	838.7	256.2	262	+ 320.5	68.7	38.2
5	1045.0	357.3	262	+ 425.7	74.9	40.7

Infant #2						
1						
2		109.8		- 109		
3	204	102.0	0.42	+ 102	99.8	50.0
4	231	174.4	29.1	+ 27.5	87.4	11.6
5	758	592.3	10.2	+ 155.5	99.7	20.5
6	536	255.0	108.56	+ 172.0	79.7	32.1
7	580	222.7	169.24	+ 188.0	70.8	32.4
8	752	315.0	56.4	+ 380.6	92.5	51.9

$$* \text{ Coefficient of absorption} = \frac{\text{N of diet} - \text{N of stools}}{\text{N of diet}} \times 100$$

$$** \text{ Coefficient of retention} = \frac{\text{N of diet} - (\text{N of stools} + \text{N of urine})}{\text{N of diet}} \times 100$$

If the absorbed and the retained nitrogen are identical amounts the subject is in nitrogen equilibrium, as is the case with normal adults on proper diets. Positive nitrogen balance occurs during periods of bodily growth, negative balance during loss of body tissue other than fat, carbohydrate, or water.

What few studies have been made^{7-9,19} during the early days of life are variable in experimental plan and thus in results; one could hardly expect them to show much agreement with each other. Differences in their outcome all the way from evidence of definitely negative balances for the first eight days after birth⁸ to evidence of large positive balances attained by the fourth day,⁷ may appear

as a result of the amount of food given. In some cases human milk has been pumped and fed without regard to the fact that colostrum is the usual neonatal food rather than the relatively protein-poor milk of later lactation. The data secured by Birk⁹ are probably the best, since he allowed his two subjects to ingest the colostrum and the succeeding milk from their own mothers. The results are arranged in Table 27. Even these figures are open to considerable criticism as to unavoidable errors: for example, the urine excreted during the first and perhaps the second day of life is in part representative of fetal rather than neonatal metabolism, and the exact point at which chemical activities of the former era can be strictly excluded from the urinary composition cannot be ascertained. The very tentative conclusions that may be drawn from Birk's and the other available data are (1) that the neonatal renal excretion of nitrogen is *relatively* small, the retention being such as to bring about a positive nitrogen balance at least by the latter part of the first week, (2) that this result is roughly related to the amount of food taken and its nitrogen content, so that positive balances occur more readily if colostrum, or cow's milk, or *enough* breast milk is fed, and (3) that such positive nitrogen balances are entirely compatible with considerable and even prolonged losses of weight from depletion of fat, water, and other materials.

Premature infants younger than two or three weeks have not been studied in this way for obvious reasons, nor is it probable that the results of studies at that age would be at all reliable. Several authors,^{8,20-24} and most recently and satisfactorily Gordon and his colleagues,¹² have brought forward evidence to show that small prematures aged one to two months on satisfactory protein intakes retain about 250 mgm. of nitrogen per kilogram of body weight per day, a figure which is about twice as great as that for the full term infant of eight days in Table 27, and indicates a better utilization of nitrogen than occurs in full term infants a month or two old. It has been shown also by Gordon's group that the retention and utilization of nitrogen by premature infants was almost unchanged when the diet was altered from human milk to cow's milk adjusted to an equivalent level of caloric and protein intake.

Is the active protein metabolism in very early life accompanied by disproportionate amounts of nitrogenous substances circulating in the blood and being excreted in the urine? The amino acids have been considered above. The urea nitrogen of the blood tends to be somewhat elevated,^{15,25-27} this concentration occurring particularly in the first half of the first week. The data of Table 28 indicate

what wide variations may be encountered. Uric acid is also increased in the blood, and there is reason to believe that certain "undetermined" nitrogen fractions of the neonatal blood are elevated as well because of their large concentrations in the urine. The non-protein nitrogen level of the newborn subject's blood, since it represents the sum of all these substances, may vary normally between wide limits but average figures have usually shown some elevation,^{4,26-28} as the table indicates. Sherman

TABLE 28
NITROGENOUS SUBSTANCES IN NEONATAL BLOOD

Author	Number and Age of Subjects		Blood Urea Nitrogen			Non-protein Nitrogen		
			Mini- mum	Max- imum	Aver- age or Mean	Mini- mum	Max- imum	Aver- age or Mean
Sherman, Pucher, Lohnes ¹⁵	(23)	1 day	10.5	22.0	15.1			
	(18)	3 days	12.9	20.0	15.86			
	(21)	5 days	9.1	18.1	14.9			
Sedgwick and Ziegler ²⁶	(4)	3 days	13.0	18.9	16.8	44.5	61.0	53.7
	(4)	4 days	14.9	22.5	17.3	39.6	52.5	46.9
	(11)	5 days	10.7	31.6	15.9	33.5	62.0	48.2
	(8)	6 days	9.4	23.5	15.6	30.1	48.1	38.4
	(5)	7 days	12.9	15.0	14.1	26.5	48.0	40.4
	(5)	8 days	8.3	13.3	10.5	32.2	50.0	37.5
	(4)	9 days	9.8	17.0	12.9	36.7	42.2	38.8
	(3)	10 days	10.6	14.0	12.1	25.2	33.3	30.4
	(3)	12 days	8.4	11.5	9.9	22.5	32.8	26.6
Adult normal range			8.0	18.0		25.0	35.0	

and his colleagues¹⁵ also measured the urea nitrogen in the blood of infants presumably normal except for the so-called inanition or dehydration fever of the newborn. The values on the third and fifth days were more than twice as great as those for the afebrile infants. Whether this change in urea was a consequence of simple dehydration or a result of the elevated temperature itself could not be proven from associated data.

Nitrogenous substances appear in the urine after birth in varied amounts, both absolutely and with relation to the total amount of urine excreted.¹⁶ The absolute amount of urinary nitrogen increases usually until the ninth or tenth day,²⁹ at first probably from

disintegration of body tissue and then from the nitrogen of the increasing protein intake; while the concentration in the urine begins at a high percentage and falls as more water becomes available for excretion. The total urinary nitrogen is the sum of a fairly constant proportion of urea nitrogen (about the same fraction as occurs in the urine of older children) plus increased amounts of uric acid, amino acid, and "rest" or "undetermined" nitrogen substances. The increase in these latter divisions is considerable and was found by Simon¹⁶ to represent polypeptides, oxypoteic acid, and other elements which may arise from incomplete metabolism of food proteins.

Creatine and creatinine have not been much studied in the first days of life. There is general agreement that the creatinine concentrations of fetal and maternal blood are almost identical at the time of birth. After birth the creatinine level in the newborn infant's blood continues at about the level for the normal adult^{26, 27} whereas the creatine may rise slightly higher,²⁶ possibly another evidence of temporarily impaired kidney function. The years of infancy are well known to be one of those periods during which creatine is normally excreted in the urine, but the younger the infant the less well-defined is his performance in this regard. The data are meager as to the degree of creatinuria in young infants^{30, 31} and almost non-existent concerning the newborn infant.^{32, 33} The creatinuria of infant subjects aged a month or more has been shown by Gamble and Goldschmidt³⁰ and others³¹ to vary with the amount of dietary nitrogen, although with reference to the diet a smaller proportion of creatine is voided in the urine of young infants prematurely born than in that of those born at term.^{31, 34} Premature infants ingesting a comparatively low protein diet such as human milk excrete almost no creatine.³¹ What little creatinuria does appear in the premature under such circumstances probably reflects an inadequacy of storage in the muscles.³⁵

Unlike creatine, which is not normally excreted by adults, creatinine appears in the urine at all ages, but its excretion is relatively less by a considerable amount in the urine of newborn infants than in that of adult men or women. Amberg and Morrill³² found the creatine coefficient $\frac{(\text{mgm. Creatinine}/24 \text{ hour urine})}{\text{Kg. body weight}}$ to be from 5

to 9 in the second week after full term birth, while average coefficients for adults are about 23 and 18 in men and women respectively. Muscular tissue, a factor of importance in determining the quantitative excretion of creatinine, is said to compose some 23

per cent of the newborn organism as compared to 43 per cent of the adult.³⁶ Nevertheless, this does not seem to be the only governing factor for there is increasing evidence that the diet plays a role in creatinine metabolism during newborn life. Apparently this is one period of normal existence in which creatinine is not wholly independent of the other elements of nitrogen metabolism.^{31,37} According to the most recent studies³⁷ creatinine excretion is even lower in the premature than in the "mature" infant.

The retention of large and perhaps irritating amounts of uric acid salts as so-called infarcts in the kidneys, and the passage of excessive quantities of uric acid in the urine, are well-known phenomena of newborn life which have aroused considerable interest.^{9,11,16,17,38} The concentrations of this substance are increased both in the blood and urine, but much more so in the latter. The amount of uric acid in the cord blood at birth is no greater than its more or less normal concentration in the blood of the mother (average 3.1 mgm./100 cc.³⁸). The blood level then gradually rises to its highest average of 3.9 mgm. upon the third day of life. This would be an abnormally high level for an adult's blood, although the inaccuracy of the methods used casts some doubt upon the degree of abnormality. It is certainly not as marked as the elevation of uric acid usually present in the urine, which is absolutely and relatively high. Adults normally eliminate 7 to 8 mgm. of uric acid per kilogram daily³⁹ which may be compared with these average figures from Schloss and Crawford.¹¹

AVERAGE DAILY EXCRETION URIC ACID PER KILOGRAM OF BODY WEIGHT

Day of Life	Group I	Group II
	Cord Ligated at Once	Cord Ligated Late
1	16.4 mgm.	16.4 mgm.
2	15.8	26.7
3	24.0	30.0
4	18.3	18.2
5	12.7	12.1
6	10.0	10.5
7	9.6	10.6
8	9.7	10.0
9	8.4	
Adult range		7-8 mgm.

Although these are the averages of data varying so widely that some come well within the normal adult range, it will be seen that on the second or third day the body may be eliminating uric acid

at three times its usual rate. The source of this substance has generally been assigned to purines originating from the nucleic acid of excess leucocytes which are undergoing destruction at this stage of newborn life. It was in an effort to prove this point that the uric acid measurements assembled above were collected after early and late cord ligation. A difficulty with the convincing application of this evidence is that the blood of these two groups of infants showed no very significant differences in leucocyte counts, and little correlation between these and the higher uric acid content in the second group at two and three days of age. Moreover Birk⁴⁰ found the time of cord ligation to make no difference in the uric acid excretion. Other explanations have been sought. Colostrum is richer in purines than is later milk;¹¹ its ingestion may have something to do with extra uric acid formation, since it is said⁴¹ that less uric acid is excreted by bottle-fed than by breast-fed infants. The meconium has been implicated as another factor.⁴² A considerable amount of uric acid, possibly from swallowed amniotic fluid, may be found there and might be absorbed through the intestinal wall during the first few days after birth. No theory has yet completely displaced the admittedly rather weak one which proposes the destruction of leucocytes as a sufficient source for so much purine nitrogen that the body is flooded with uric acid.²⁵

Probably the relatively impaired state of neonatal kidney function may have a general bearing upon the formation of infarcts, for these occur even when the uric acid itself is being excreted in amounts not absolutely excessive.¹⁰ It is interesting in any case to remember that the rise in excreted uric acid is relatively much above that of blood uric acid, so that apparently the body's powers of clearing the substance from the blood are not at all overwhelmed, even though infarcts incidentally occur in the kidneys. Moreover, there is no evidence whatever to show that either the moderate post-natal rise in blood uric acid, the effort of excreting it in large amounts, or the formation of its crystals into infarcts, does any important harm to the infant. The general analogy between uric acid infarction and the state of kidney function on the one hand, and icterus neonatorum and the state of the liver on the other, is an attractive one. In fact, the possibility of a specific relationship between these simultaneous excesses of uric acid and bile pigment has been explored by Berger,⁴³ but without the demonstration of any parallelism between quantitative measurements of the two substances in a large series of cord bloods.

It is perhaps improper to consider the circulating proteins of the blood at this point, so independent are their concentrations from

the transient changes of nitrogen metabolism in general, but something may be said of the subject here to prepare for further remarks under the physiology of water distribution and excretion in a later chapter. Results of some of the standard investigations are listed in

TABLE 29
THE BLOOD PROTEINS OF INFANTS

Author and Date	Method	Material	Age and Number of Subjects	Gm./100 cc.		
				Maximum	Minimum	Average
Pommerenke ²	1936 Micro-Kjeldahl	Plasma	Birth 40	6.31	5.46	5.89
Ruiz ⁴⁷	1912 Refractometry	Serum	1 day 9	6.98	4.60	5.78
			2-3 days 13	6.77	4.70	5.78
			11-15 days 6	6.34	5.31	5.78
			2-12 wks. 19	7.48	4.96	6.12
Utheim ⁴⁸	1920 Refractometry	Serum	1 day 14			6.25
			2 days 12			5.80
			3 days 12			6.33
			5 days 13			5.59
			10 days 3			6.19
			1 month 3			6.29
Bakwin ⁴⁹	1922 Refractometry	Serum	Birth-7 day 125 (slightly higher 1st, 2nd, 3rd days)			6.5
Ray & Phatak ⁵⁰	1930 Colorimetric	Serum	5-22 days 26	7.83	6.26	7.04
Marples and Lippard ⁵¹	1932 Refractometry	Serum	1-9 days 40	7.71	5.14	6.24
Andersch and Oberst ⁵²	1936 Micro-Kjeldahl	Serum	Cord blood 25	7.7	5.3	6.4
Denzer, Reiner, Weiner ⁵³	1939 Refractometry	Serum	Cord blood 79	7.43	5.15	6.04
			1-2 days 17	7.02	5.10	6.03
			3-4 days 20	6.67	5.15	5.89
			5-6 days 21	7.01	5.10	6.02
			7-8 days 15	6.60	5.10	5.93
Darrow, Cary ⁴⁵	1933 Kjeldahl	Serum	"Newborn" 20	7.0	4.5	5.52
			5-6 mos. 14	7.0	5.8	6.29
Rapoport et al. ⁴⁶	1943 Micro-Kjeldahl and Salt Preparation	Serum	First 2 days 17			5.11
			2-11 mos. 16			6.10
—PREMATURE INFANTS—						
Darrow, Cary ⁴⁵	1933 Kjeldahl	Serum	6-90 days 26	7.0	3.8	4.94
Rapoport et al. ⁴⁶		Serum	1-68 days 17			4.55
Young, et al. ⁵⁴	1941 Micro-Kjeldahl	Plasma	3-5 days 12	5.36	3.62	4.62
			8-18 days 8	5.02	3.80	4.42
			Premature infants with edema: 2-7 days 6	5.04	3.73	4.54

Table 29. During fetal life the total plasma or serum proteins of animals are less concentrated than in the maternal blood at the corresponding stage of pregnancy;⁴⁴ this also appears to be the case with the human infant at the time of birth, as is indicated by Pommerenke's analyses presented in Table 25. Discussion requires consideration of the albumin and globulin fractions, for which data have been made available by Darrow and Cary⁴⁵ and by Rapoport

and his colleagues.⁴⁶ Study of these reveals a consistent tendency for the somewhat low total protein values at birth to result essentially from globulin deficiency. In this regard the premature infant displays a particular shortage as is shown in the diagrams of Figure 29. It is noteworthy that the data in Table 25 indicate a quantita-

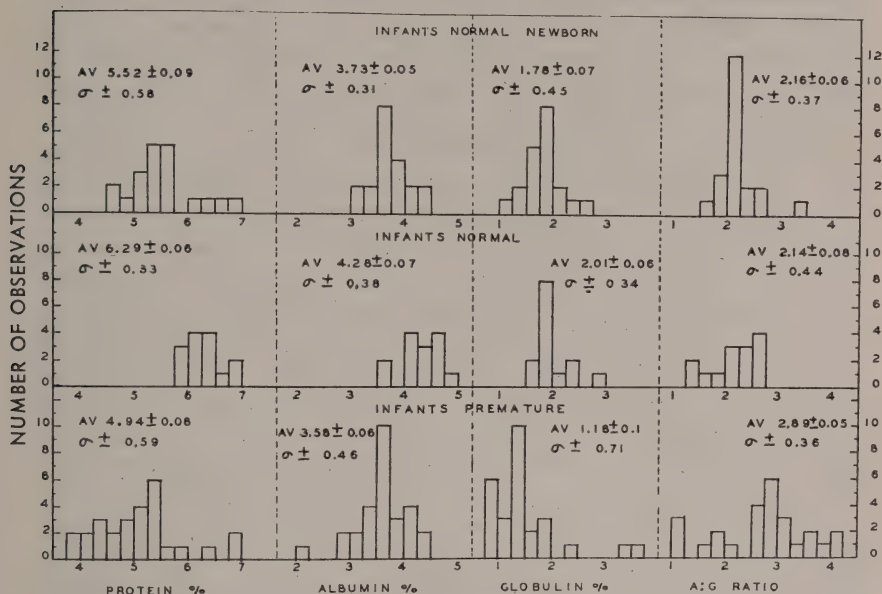


FIGURE 29

The total and fractional serum proteins of newborn infants, older infants aged 4-6 months, and premature infants aged 6-90 days. (Darrow, Cary, J. Pediat. 3: 573, 1933.)

tive difference between the globulin in the umbilical artery and that in the umbilical vein at birth, the latter being well above the former. Why this should be the case is somewhat mysterious. It suggests that the blood is replenished with globulin during its passage through the placenta, yet it has been shown that the euglobulin fractions, at least, cannot cross from the maternal into the fetal blood.^{55,56} In fact, the probability is that all the protein molecules are independently produced and independently regulated properties of the two organisms. Information as to the nutritional function of the placenta might be gained by a further study of this point.

The generally lowered blood proteins at birth tend to require weeks or months before their concentrations begin a gradual in-

crease. Darrow and Cary,⁴⁵ who quote further evidence on the problem,⁵⁷ suggest that the globulin deficit in early life may be related to a lack of those stimuli (such as infections) which normally call forth the production of globulins in older subjects. This is in agreement with the paucity of euglobulin at birth. If the albumin fraction were the depressed one, the protein deficiency of newborn infants would be much more likely to lead to a state of edema. Actually a neonatal edema from hypoproteinemia can rarely be suspected except in prematures, and even there the evidence is far from clear. In Table 29 it will be noted from Young, Hallum and McCance's data⁵⁴ that edematous premature infants present practically the same plasma protein concentrations as do normal ones, although these authors quote Hallum as having found the concentrations in some edematous infants as low as 2.7 gm. per cent. In several of these subjects the concentration of protein was said to have increased as the edema disappeared. On the other hand, no apparent relationship existed between edema and plasma proteins in prematures studied by Hickmans and her colleagues.⁵⁸ Fractional analyses of proteins in edematous and non-edematous premature infants are not available. In general, when one considers the dietary and other variations to which even normal newborn infants are subject, the serum proteins seem to be the objects of fairly reliable regulation by the body. On the other hand there is no obvious reason, unless it be the immaturity of the organism or the demands of growth, to explain why their concentrations are less than those of older subjects.

CARBOHYDRATE ASSIMILATION AND METABOLISM

Carbohydrate metabolism is a somewhat less complicated subject than protein metabolism, for the substances concerned exist in fewer and simpler forms in the body. Nevertheless the controlling forces of endocrine physiology are neither simple nor completely understood, nor are all aspects of glucose-glycogen-lactic acid relationships entirely agreed upon. The following discussion therefore will be limited to a description of the adequacy with which carbohydrate foods are handled by the digestive tract of the newborn infant, and to a summary of the sugar concentrations normally to be expected in fetal and neonatal blood. Mathematical balance sheets for protein utilization can be constructed from the nitrogen of the food, stools, and urine, but carbohydrate can be traced (for present purposes) only by determining the alterations in the blood which follow its ingestion. It may be best to consider the general subject of blood sugar at the outset and later to draw what inferences seem allowable as to digestion and absorption.

It will be recalled that the infant at birth is using carbohydrate almost exclusively for heat production, although very soon thereafter a period of three or four days is begun during which fat combustion replaces two-thirds or more of the carbohydrate utilization. Almost certainly the major source of fetal energy has been carbohydrate. Knowledge of the mechanisms involved rests upon an insecure foundation of inadequate data. Although glucose passes from mother to fetus across the placenta, this does not occur by easy diffusion. The sugar concentration in the fetal blood at term, and probably before, has, with few exceptions,⁵⁹ been found to be lower than that in the mother's blood.⁴⁴ The fetal blood sugar appears to alter with development; in animals with short gestational lives the level has been shown to increase during intra-uterine growth by more than 100 per cent, but still to fall short of the maternal concentration.⁶⁰ The amounts in the two circulations seem to be neither wholly independent of each other nor, on the other hand, closely related. Although the placental systems are not alike in all mammals, so that observations upon one species need not apply to another, no work has yet shown that blood sugar changes on one side of the placenta are reflected in simultaneous alterations on the other. Studies upon animals⁶¹ in which such changes were artificially produced showed no correspondence between the maternal and fetal bloods thereafter. Alimentary hyperglycemia brought about in human mothers just before delivery has been followed by sluggish and only partial adjustment on the part of the fetal sugar level.^{62,63} It is probable that the fetus has two sources of available carbohydrate, for besides that which crosses over from the maternal blood sugar, a portion may come (by an ill-understood mechanism) from glycogen deposits in the placenta itself. During the first third of gestation that organ is increasingly rich in glycogen, whereas with increase of fetal age thereafter the placental glycogen steadily diminishes while the glycogen content of the fetal liver is being as steadily augmented.^{64,65} Thus as term approaches, the fetus takes upon itself more and more of the management of carbohydrate economy and becomes less and less a simple parasite living directly on maternal and placental glycogen and glucose.

Numerous attempts^{26,27,61-73} have been made to establish the normal sugar content of the blood at birth and in the early days thereafter. In general the resultant data are marked by wide and confusing variations, differences occurring from the use of conflicting methods for blood collection and measurement, and from a characteristically wide range of glucose concentration. So wide is this range that a "normal" figure is of little value. However, independent investigations have shown essentially similar trends.

Since, among the three most recent studies, those of Hartmann and Jaudon⁷¹ and of McKittrick⁷³ were presented largely in graphic form, we show here a tabulation derived from Ketteringham and Austin's measurements. The method which was used, that of Folin and Malmros, gives blood dextrose values for normal adults ranging between 70 and 90 mgm. per cent. Even though the cord blood average of 103.6 is above this range, the maternal specimen obtained at delivery usually showed sugar concentration some 20 mgm. still higher. The decline and wide scatter after birth is obvious, as is a rising tendency by the third day. This continues, as

TABLE 30
BLOOD SUGAR VALUES IN THE NEWBORN
(From Ketteringham and Austin⁷²)

Age	Birth (Umbilical Vein)	3-6 hrs.	1st day	2nd day	3rd day
Number of Cases	47	10	45	41	42
Blood Sugar (mgm./100 cc.)					
Mean	103.6	66.8	68.3	70.3	76.1
Normal Range*		55-75	55-75	55-75	65-85
Highest of Series		79.1	102.2	102.9	110.3
Lowest of Series		56.9	46.6	52.4	57.1

* Normal range for adults, this method, 70-90.

other investigators have shown, in a slow increase and a gradual narrowing between the minimal and maximal values. This perhaps indicates that the blood sugar is being brought under one set of regulatory mechanisms and is not, as at birth, a product of both maternal and fetal functions. By the end of the second week an average concentration little different from that of adults is reached. The declining glucose levels of the immediate postpartum period may and often do fall into an area which would be considered distinctly hypoglycemic in adults. The lack of characteristic physical symptoms in newborn infants with so little blood sugar has been commented upon by others and is worthy of emphasis in view of the assumption often made that various disturbances in the babies of diabetic mothers may be assigned directly to hypoglycemia. It may be that the neonatal state confers a relative resistance to hypoglycemic stimuli just as it does to anoxia.⁷⁴

While no relationship has been demonstrated between blood sugar and birth weight in full term infants, the few studies on the blood of premature infants usually have shown glucose concentra-

TABLE 31

BLOOD DEXTROSE IN PREMATURE INFANTS⁷⁷
 (Hagedorn-Jensen Method—Adult Normals = 80–110)

Patient No.	Birth Weight (gm.)	Age	Weight (gm.)	Fasting Blood Sugar (mgm.%) (4–5 hours after feeding)
1	2,280	5 days	2,100	33
2		12 days	2,280	65
3	2,180	5 days	2,040	27
4		12 days	2,200	62
5	1,570	23 days	1,640	66
6		30 days	1,750	75
7	1,670	23 days	1,680	50
8	1,720	3 days	1,560	47.5
9		10 days	1,660	74
10	1,570	17 days	1,810	64
11		3 days	1,470	47.5
12	1,570	10 days	1,540	81
13		17 days	1,650	69
14	1,860	32 hrs.	1,790	54
15		7 days	1,900	47
16	1,300	14 days	2,180	49
17		1 mo.	1,770	48
18	1,970	6 wks.	2,010	63
19		2 days	1,710	51
20	2,060	9 days	1,860	66
21		27 days	2,160	82
22	2,060	42 days	2,530	90
23		2 days		32
24	1,840	30 days	2,510	71
25		4 days	1,750	49
26	2,070	11 days	1,800	69
27		2 days		60
28	1,780	9 days	2,130	60
29		16 days	2,250	69
30	1,780	42 days	2,800	68
31		3 days	1,670	49
32	1,780	17 days	2,040	43
33		30 days	2,250	60

tions still lower than those found after full term birth. In a minority of observations^{69, 75} this was not the case. Haass⁷⁶ concluded that the lowering of blood sugar in prematures was related more to the temperature of the infant than to its weight or gestational maturity; indeed his protocols show that quite regularly the infants became much less hypoglycemic as their temperatures were brought up, and this often occurred within an interval so short that little "development" of regulating centers could possibly have taken place. Van Creveld⁷⁷ also found low blood sugar values in premature infants. While he unfortunately does not mention the body temperature of his subjects he gives the impression that the subsequent rise in these figures was so gradual as to make changes in temperature of no significance in their explanation. His data are reproduced in Table 31. It was his general conclusion that this peculiarity of premature infants was not due specifically to hyperinsulinism, starvation, deficiency of liver glycogen, or any specific factor other than general functional immaturity.

The response of the newborn infant's absorptive and assimilative powers to the ingestion of carbohydrates is attested by a few studies. Svensgaard⁷⁸ performed glucose absorption tests on a group of infants during the first eight days of life and then repeated the procedure with the same subjects five to nine days later. Most of the curves obtained at the younger age showed a sluggish but definite rise, the peak values differing from the fasting ones by an average of 47 mgm. per cent. On the other hand the elevation of blood glucose after similar tests a few days later was fairly regularly a higher one, so that its average extent was 82 mgm. per cent. This difference in performance was not related to alterations in the weight of the subjects between the two tests; the fasting blood sugar levels were not significantly different in the two groups, nor was there a difference in the average time at which the peak values were attained although the induced hyperglycemia was usually of longer duration in the older subjects. Until data are available as to the results of intravenously administered glucose these results cannot be accepted as proof of a deficient adsorption from the bowel, or as an effect of characteristically sluggish gastrointestinal motility in neonatal life. Ketteringham's⁷⁹ curves of neonatal sugar absorption cannot be compared with the findings just mentioned because her work did not include repeated tests on the same infants. Of considerable interest in data secured through a four hour period after the test dose is the newborn subject's ability to recover his blood sugar level after the falling limb of the curve has dropped below the original fasting level, as it frequently does by three hours.⁷⁹

This compensatory rise in the four hour specimen speaks for a good regulatory capacity, or at least for the ability of the infant to react successfully to both elevation and depression of blood sugar. In general the response to ingested glucose in newborn infants is thus not strikingly different from that in older children.

Greenwald and Pennell⁶⁷, however, have found somewhat lower curves for a group of 15 infants aged from 4 to 9 days than they considered normal for older infants, whose curves were again lower than those of adults. These authors made a useful contribution to the subject by measuring the blood sugar changes after similar amounts of sugars other than glucose were fed, and also after ordinary breast feedings. The concentration of glucose in the blood appears to be greatest after the ingestion of pure glucose itself, very little less after feedings of such disaccharides as saccharose (cane sugar) and lactose, while a somewhat lower and more protracted rise followed the administration of a maltose and dextrin mixture. Since all these carbohydrates are absorbed almost entirely as monosaccharides it is evident that the enzymes capable of splitting the disaccharides into their simpler elements must be abundantly present in the alimentary tract at or soon after birth and that the adsorption of simple sugars is fairly easy and prompt in the newborn. Breast milk contains carbohydrate in the form of lactose, together with its other food substances. In infants of more than four days from birth, nursing was always found to cause an elevation in blood sugar, although the rise was neither so rapid nor so high as after pure sugar solutions were fed. The actual amount of carbohydrate ingested in these nursings was perhaps lower than in the other tests. Not only has the adequacy of sugar-splitting enzymes been demonstrated by such absorption or tolerance studies, but some evidence has been obtained by Bentivoglio⁸⁰ that a mild elevation of blood sugar follows even the ingestion of pure starch by some newborn infants, so that amylolytic enzymes as well as those digesting simpler carbohydrates can perhaps be present to some degree at this age.

Van Creveld⁷⁷ has shown that the blood sugar of premature infants aged three or more weeks rises after glucose ingestion in a manner not different from the response of mature infants. Premature subjects with considerable hypoglycemia after fasting tended to display relative hyperglycemia after the test meal. No work has been found in which the assimilation of lactose ingested by the premature has been measured. Such data would be of some interest since it is claimed⁸¹ that lactase is the last disaccharide-splitting enzyme to appear in fetal development and that it is absent or

exists only in small amounts in the intestine until the eighth fetal month. However, there is evidence^{82, 83} to show that normal premature infants have considerable ability to increase their secretion of lactase depending upon the amount of lactose fed. After a large alimentary increase, lactose may even be absorbed unsplit into the body of the premature and excreted by lactosuria, but such infants seem to accommodate quickly by the formation of the necessary amount of enzymes after a very few days of high lactose consumption.⁸²

The urine of infants subjected to glucose absorption tests has not been examined, so that nothing can be said as to the "renal threshold" for glucose at this age. An early study by Grosz⁸⁴ describes the finding of what was presumed to be lactose in the urine of young infants after feedings containing more than 3.3 gm. of lactose per kilogram. No blood sugar levels were published. This is somewhat more lactose than would be offered to a newborn infant in an ordinary bottle or breast feeding. It was at one time claimed⁸⁵ that glycosuria often occurred in infants delivered somewhat traumatically, but this was later disproven by Lindig.⁸⁶ He found only a very transient glycosuria in 3 of 24 infants delivered by forceps, whose urines were examined for seven days after birth. None of the other subjects voided urine containing any sugar. Nor has sugar been found in the urines of premature infants during a like period.⁷⁵ Since the mild hypoglycemia of mature infants and the somewhat more severe hypoglycemia of prematures is not referable to urinary excretion and probably not to poor absorption, its chief causes must be the relatively insufficient amount of dietary carbohydrate and of stored glycogen available at the beginning of newborn life, and perhaps also the disturbed functioning of the liver, the pancreas and other glands producing internal secretions.

In conclusion, there would seem to be no doubt that the cells of an organism, which has just completed several fetal months during which it was sustained largely upon carbohydrate, are able to utilize glucose well. It is also apparent that in the first few weeks of extra-uterine life the absorption of digested carbohydrate from the bowel is a smooth and speedy process. Digestion of such food substances, if less complex than starch, offers no difficulties. After regular feeding is well established a large proportion of food may be made up of carbohydrate. Even for small premature infants, Levine and Gordon⁸⁷ advocate feedings which contain considerably more carbohydrate than would be furnished by human milk. Immediately post-natal blood glucose measurements offer grounds for some speculation. In the light of present knowledge it would seem

wiser to accept "hypoglycemia" after birth as an almost physiological probability, rather than to encumber the asymptomatic infant with an extra load of sugar, by whatever route, in an attempt to correct this situation. And it is suggested that in the infant with abnormal symptoms careful attention be given to all other possibilities before their cause is decided to be hypoglycemia.

FAT ASSIMILATION AND METABOLISM

Less is known of fat metabolism than of the body's dealings with the other sources of nutrition, and this ignorance as to the general subject limits what can be said of any particular aspect. For the fetal and newborn periods of life the mathematical data, although from reliable sources, are themselves meager, so that the foundation for an understanding of neonatal fat metabolism is not a broad one even were sound principles of interpretation at hand. All that can be attempted is a presentation of the facts now available, in the hope that as further work illuminates the general subject the significance of these facts will become more apparent. It is still necessary to be as honest as Dr. Morse and Dr. Talbot were in 1915,⁸⁸ when they put the reviewer's position thus: "Despite these facts, it seems wise to summarise what *we think we know* about the digestion and absorption of fat." The aptness of this wording merits the italics which have been added.

At the outset it should be noted that fat does not lend itself well to measurements of absorption based upon the arithmetical difference between that which is present in the food and that which can be found in the feces. Fat not only appears in the latter situation as an unabsorbed residue from the former, it also appears there as an excretion from the body. Therefore what is described by such a subtraction is not absorption but retention. Nevertheless the percentage of fat so retained can be used as a rough indication of *minimal* absorption. Even here the body's transformative powers make any very close reasoning impossible, because not all of the fat with which it deals originates as such in the diet. The body can and does make fat from protein and carbohydrate.⁸⁹

At the time Morse and Talbot were writing, about thirty years ago, the general consensus of investigators was that the fat absorption of infants, however they were fed, was very high. A series of measurements by various workers indicated that babies normally absorb anywhere from 92 per cent to more than 99 per cent of dietary fat.⁸⁸ However, only a few studies have been discovered of which the subjects could be called newborn infants. A baby is mentioned by Wacker and Beck⁹⁰ who, during the third week of

life, absorbed between 85 and 88 per cent of the fat ingested. Holt, Courtney and Fales⁹¹ found a figure of about 95 per cent in two subjects aged three and three and one-half weeks. The later work of L. E. Holt, Jr., and his colleagues⁹² indicates that the younger the infant the nearer to 80 is the percentage of dietary fat retained. In their studies they showed that butter fat was less completely retained from the food than was the fat of human milk. Even the latter substance does not appear to be as satisfactorily retained in very early infancy as it is somewhat later. This mild deficiency of fat retention by newborn infants is not sharply limited to the neonatal period, for the percentage of retention becomes higher only gradually throughout the first year of life.

Fat retention in premature infants is generally lower than in "mature" ones, although there is some disagreement as to the relative use made of the various sorts of food fats. Tidwell, working with Holt's group,⁹³ found that when butter fat, olive oil, and soy bean oil were fed in separate periods to premature subjects, the average retentions were 58 per cent, 72 per cent and 83 per cent respectively. There were no regular differences corresponding to the ages and weights of the infants studied, so that individual differences must apparently be more responsible for the efficient use of fat than is relative maturity. Still more recently Gordon and his colleagues⁹⁴ have confirmed these general findings and have shown that while full-term infants aged from two weeks to two months waste in their stools about 25 per cent of the fat fed in cow's milk mixtures (and 10 to 15 per cent in the case of olive oil fat) premature infants lose an average amount of about 47 per cent of cow's milk fat by way of the feces. Feeding of human milk to a similar group of premature infants was accompanied by a fecal loss of about 30 per cent of the fat content. It is probable that variations of this degree are to be assigned to difference in uptake from the alimentary tract and not in any important respect to varying excretion through the bowel wall, though this is difficult to prove. Again, the inability of these subjects to absorb and retain fat did not correspond to their individual ages and weights but seemed to be a general feature of prematurity. Since the failure of absorption was conclusively shown to be related to the amount of dietary fat, a much larger proportion being wasted on high intakes than on low, Gordon has repeatedly advocated the adjustment of foods for premature infants toward a fat intake about half that usually comprised either in human milk or in cow's milk formulae. In Levine and Gordon's recent lectures very interesting data¹³ are presented to show that whatever the cause of this defect of the premature, it

does not arise from a failure of digestive enzymes to split fats in the bowel, since the fat wasted in the feces is equally great whether its content of split fat be 90 per cent or more as may be the case when cow's milk is fed, or less than 60 per cent as may occur during olive oil feeding. Table 32 reproduces the relevant data. It is likely that the less severe discrepancy in fat absorption present in the full-

TABLE 32
RELATION OF TYPE OF FAT IN DIET TO FECAL FAT¹³
(Observations on four subjects)

Type of Fat in Diet	Fecal Fat		Fecal Fat	
	Gm./Kg.	Percent- age as Split Fat	Gm./Kg.	Percent- age as Split Fat
Subject:	M.S.		B.H.	
Olive oil	2.7	63	2.1	55
Cow's milk	2.6	92	1.9	88
Olive oil	2.6	58	1.3	65
Subject:	I.S.		T.M.	
Cow's milk	1.2	93	1.7	93
Olive oil	0.7	67	1.5	56
Cow's milk	1.0	89	1.1	92
Weight and age of subjects:				
M.S.	B.H.	I.S.	T.M.	
1.5 to 1.9 kg.	1.8 to 2.5 kg.	1.8 to 2.4 kg.	1.9 to 2.4 kg.	
13 to 32 days	16 to 35 days	12 to 28 days	9 to 25 days	

term newborn infant may be ultimately laid to the same cause as that which more greatly hampers the premature infant in this regard.

Since the time of Tobler and Bogen's observations in 1909⁹⁵ (if not, indeed, before) fat substances in foods have been supposed to delay the emptying time of the stomach and to retard intestinal motility. With the newer knowledge of the wide variations normal for these processes, it appears that this point is largely of academic importance. It has recently been stated by Ivy⁹⁶ that "there is insufficient fat in either normal human milk or cow's milk to have an inhibitory effect on a normal infant's stomach."

Discussion as to the fate of fats in the body must touch upon pre-natal conditions. It is known that the adipose tissue of the fetus as

well as that of the newborn infant has different characteristics from that in the body of the mother and of adults in general. Neonatal fat has a higher melting point and a higher proportion of volatile fatty acids than that of the body in later life. Since lipid substances are now known to be in a constant state of flux in the tissues, being absorbed, broken down, formed and reformed from proteins and carbohydrates as well as from other fats, the origins of these differences have become less mysterious than they once were. Fetal fats, whatever individual characteristic they may have, must in some part originate from the fats of the mother's blood, since the cord blood leaving the placenta to supply the fetus in the umbilical vein is regularly higher in certain lipid materials than is that arriv-

TABLE 33
FATS OF HUMAN FETAL BLOOD⁹⁷
(mgm./100 cc. citrated whole blood)

	Umbilical Artery (Fetus to Placenta)	Umbilical Vein (Placenta to Fetus)
Average Phospholipid	160	204
Average Free Cholesterol	55	64
Average Ester Cholesterol ¹	8	13
Average Neutral Fat ²	116	121

1. Ester cholesterol is not taken up by the fetus when the concentration in the umbilical vein blood is below 10 mgm.; under such circumstances some may be released from the fetus to the mother (Boyd and Wilson).
2. Neutral fat may, without apparent reason, be higher in the umbilical artery than in the vein (Boyd and Wilson).

ing at the placenta in the umbilical arteries. Boyd and Wilson⁹⁷ have shown this very clearly in the averages of measurements from the cord vessels of 15 infants at delivery (Table 33).

Since all that is known of the respiratory quotients of fetal and neonatal life suggests that carbohydrate is the almost exclusive source of fetal energy, it appears that most of this uptake by the placental circulation is for purposes of storage and essential or "operative" cellular requirements. It is probable, as stated above, that the fetus also synthesizes some fat for these purposes from its supplies of amino acids and carbohydrates. At just what rate storage of fat takes place in the human fetus has not been quantitatively determined, but it is interesting that the liver of the guinea pig at birth has acquired from four to six times as much fatty acid (per gram of liver) as is present in the liver of the adult animal,

only to have this surplus rapidly removed during the first few days of extra-uterine life.⁹⁸ Thus fat, as well as glycogen, is stocked in the liver (and probably elsewhere) apparently against the needs of the post-natal period; moreover, the placenta seems to provide some lipoids which are increasingly drawn upon by the fetus during its development, just as is the case with placental glycogen.

The blood fats of the mother are gradually increased during pregnancy, so that at term they are very definitely elevated on the maternal side of the placenta. On the other hand, the blood of the newborn infant differs from the normal in the opposite direction; as a result the cord blood at birth contains much smaller concentrations of lipid substances than that of the mother, which testifies strongly against any easy passage of these materials across the placenta.⁹⁹⁻¹⁰³ These relationships are shown in the following table.

TABLE 34

AVERAGE AMOUNT OF VARIOUS FATS IN MGM./100 CC. OXALATED PLASMA

	Adult*	Pregnant Woman at Term**	Newborn Infant*
Total Lipoids	589	780	198
Total Fatty Acids	353		140
Neutral Fat	154	315	90
Phospholipid	196		61
Free Cholesterol	47		14
Cholesterol Ester	192		20
Cholesterol	223***		120***

* Adapted from Boyd(103).

** Gentili (102).

*** Rosenbloom (101).

From these low concentrations at birth there appears to be a rapid increase in all circulating fat substances during the next few days of life. The values are subject to much wider deviation than even those characterizing the blood fat measurements in adults, but the tendency in early life (just as with the concentrations of blood sugar) is for the fat concentrations to become relatively less divergent as the individual figures are augmented.

This neonatal rise in the plasma lipoids and their relationship with adult values is shown well by the data of Senn and McNamara,¹⁰⁴ which, since heparinized plasma was used, gave slightly higher values than those quoted in the preceding table:

TABLE 35
ADJUSTMENT OF BLOOD FATS IN NEONATAL LIFE¹⁰⁴

	1-13 Hours		6-10 Days		Adults	
	Range	Mean	Range	Mean	Range	Mean
Total Lipoids	119-331	221	297-651	468	450-1260	735
Neutral Fats	8-149	80	92-268	173	50- 580	225
Phosphatids	0- 94	27	19-190	103	60- 335	181
Free Cholesterol	23- 44	32	37- 68	51	56- 121	82
Cholesterol Esters	47-128	82	103-189	142	86- 440	247

Not many measurements are available to show how much of this general elevation takes place in the immediately post-natal days before the intake of food can be expected to provide large new supplies of fat from outside the body. In view of the changes in respiratory quotients, according to which life seems to be sustained by a metabolic mixture containing 80 or 90 per cent fat during the third to fifth days after birth, it is small wonder that fat makes an increasingly prominent appearance in the blood stream, so that most of its elements are at least doubled in concentration by the second week. Evidence has been brought forward¹⁰⁴⁻¹⁰⁵ that these increases are not in any important degree the result of dehydration of the blood. For obvious reasons no data have been secured upon the blood fats of infants fasted for any longer than eleven hours; but after an interval of that length the blood fats appear to be somewhat lower than after shorter periods without food, though still well above the low level at birth.¹⁰⁴ Thus the neonatal changes in fat metabolism cannot be due entirely to an increased tide of absorption, and the tendency to a wide scatter of normal values is probably not incurred from variations of intake but reflects a natural instability of regulating mechanisms in the course of a great and sudden increase in the importance of fats to the body.

The available knowledge is so vague that discussion of the separate lipid substances is not very profitable, while analysis of the significance of their changing concentrations is scarcely possible. With regard to cholesterol, Sperry¹⁰⁵ has shown that the greatest share of its increase in total amount takes place during the first three or four days after birth. Indeed in some of his subjects the cholesterol concentration fell off slightly after the fourth and until the twenty-fifth day. Notwithstanding the supposed relationship of the liver to cholesterol metabolism he could find no particular alterations in infants with icterus neonatorum. The ratio between combined (ester) and free cholesterol, which is quite constant in

the plasma of adults and tends to be much less stable but generally lowered in the newborn period, was not especially altered in icteric infants. Dr. Sperry himself is unwilling to interpret any of these facts except, again, as showing disturbance of general adjustment.

A table adapted from Senn and MacNamara¹⁰⁴ is helpful in presenting the inter-relationships of certain plasma lipids in infants and adults. The percentages indicate the average fraction represented by the individual substance in the total plasma lipid mixture at the given age. It will be noted that the only appreciable difference between the blood fat picture of infants in the second week and of adults is the somewhat higher percentage of neutral fats of the former subjects. Since an increase of neutral fats in the blood is generally most marked following a fat-containing meal, the increase in this fraction may have to do with the direct energy-producing function of fat metabolism, but whether it reflects a period of large alimentary absorption or organic synthesis, or an insufficient utilization or storage cannot be stated. A few sentences from Peters and Van Slyke may throw some light upon the two- to three-fold increase in most blood fats which marks the first two weeks of life, and upon the relative excess in neutral fats of neonatal as compared to adult physiology. "If diets are well balanced any one of the chief food constituents can be varied within wide limits and over long periods without altering the post-absorptive concentration of blood lipoids. The mere addition of an unusually large amount of fat to an otherwise normal diet does not necessarily cause hyperlipemia except immediately after the meal. . . . It seems probable, as Campbell has suggested, that durable increases of blood fat result not when more fat enters the body to be burned or conveyed to storage depots, but when there is a continuously greater demand for fat as fuel because of the absence of available carbohydrate."³⁹ Certainly one of the metabolic adjustments of neonatal infancy is to relinquish an almost purely carbohydrate energy supply in favor of a mixed combustion of carbohydrate and fat.

TABLE 36
PERCENTAGE COMPOSITION OF TOTAL LIPIDS

Age	Total Lipids mgm./ 100 cc.	Phospho- lipids	Cholesterol		Neutral Fats
			Free	Esters	
1-13 hrs.	221	11.0%	15.0%	40.0%	34.0%
6-12 days	468	21.0%	11.0%	32.0%	36.0%
Adults	735	23.6%	11.8%	35.4%	28.2%

CLINICAL SUMMARY

To summarize the digestive and absorptive processes first, the infant, whether premature or full-term, seems to have most facility in dealing with proteins. The reverse is true of fats, although the difficulty does not appear to be a want of digestive enzymes for that substance. Carbohydrates less complex than starches appear to reach the blood stream as dextrose during neonatal life with almost equal rapidity and in almost the same quantity after eating, whether they be monosaccharides or disaccharides.

What happens to the various food substances after absorption requires a separate discussion. As to **protein**, the infant has been shown by balance experiments to excrete in the urine a *relatively* small amount of nitrogen, so that a positive nitrogen balance normally obtains by the end of the first week, this being more predictable if large rather than small amounts of protein are fed. As a result of several circumstances which include the intake of food, the various non-protein nitrogenous components of the blood tend to be elevated during the first 5 to 10 days of life. Figures of 50 to 60 mgm. per cent may be obtained in blood non-protein nitrogen measurements from quite normal infants. Although uric acid is somewhat increased in the blood it is especially concentrated in the urine, so that values of 3 or 4 times the adult figure may normally occur during the first post-natal week. Whatever the cause of this tide of uric acid, one result is the common finding of probably harmless "uric acid infarcts" in the neonatal kidneys; another is the pink color which excess urate salts impart to the infant's urine and diaper.

The nitrogenous substances just discussed undergo neonatal variations during a comparatively brief period. The blood proteins are subject to somewhat less profound but more persistent deviations from the concentrations normal for older subjects. In general, these produce a diminution of about 1 gram per 100 cc. of serum or plasma, so that the usual serum or plasma protein value during (and for some time after) the newborn period is about 6 gm. per cent or less. This deficiency, largely traceable to the globulin fraction, is still more marked after premature birth, so that the total serum proteins of premature infants tend to average about 4.5 gm. per cent. Since it has not yet been shown that this is the determining factor in causing the occasional edema of prematures, there is little reason for attempting to overcome such a clinical condition by supplying extra protein through intravenous or alimentary routes until the individual infant has been carefully studied. The significance of the globulin deficiency may be largely immunological, and will be discussed further in a later chapter.

Since the fetus apparently utilizes **carbohydrate** as its main, if not its only, source of energy, it is understandable that dextrose is handled efficiently once it has reached the blood. As stated above, the apparatus for the digestion of disaccharides (milk and cane sugars), and that for monosaccharide (dextrose) absorption, is in satisfactory working order very soon after birth. Supply and regulation are such that a wide range of blood sugar measurements has been obtained; following an immediate post-natal fall the concentrations may vary between 40 and over 100 mgm. per cent during the first few days of life. Although the blood sugar levels of prematures tend to fall still lower, newborn infants in general show so few symptoms of hypoglycemia that a peculiar neonatal tolerance to low blood sugar may be suspected. Caution should therefore be used in concluding that untoward manifestations of infants born to diabetic women are necessarily hypoglycemic in origin. Glycosuria occurs no more frequently in newborn infants than in older subjects.

Although unexplained difficulties stand in the way of the efficient absorption of dietary **fats**, the metabolism of lipid substances undergoes a sudden increase in activity soon after birth. The fetus probably uses little fat for its heat production but stores a considerable amount against later emergencies; how this is brought across the placenta is not known. Once the newborn infant has fairly well depleted its available glycogen stores (which is usually within a few hours after birth) it begins to depend largely upon reserves of fat for energy. During this process there is a greatly increased transport of fat substances in the blood, an increase not solely due to the newly introduced element of absorption from the alimentary tract. While the concentrations of most varieties of blood fats are roughly doubled between birth and the second week of life, they still do not reach the levels characterizing later life. Thus, these increases give more testimony to the relatively minor role of fats in body activity before birth than to an absolutely inordinate degree of neonatal lipid metabolism.

The high protein and low fat contents of colostrum are in keeping with what has been learned as to the degree of digestibility and utilization of foods at this period. There are physiological reasons for believing that fat in the artificial feeding of the newborn ought to be subject to some limitation, which would allow the utilization of more easily digested and absorbed other foods. Experience and experimentation have shown that formulae based upon partially skimmed milk, with calories derived particularly from protein and carbohydrate, are probably the most nourishing for newborn full-term infants and for prematures, providing that breast milk cannot

be obtained. Substitution of olive oil for butter fats in the feedings of prematures has been shown to result in less wastage of fat in their feces.

BIBLIOGRAPHY

1. SLEMONS, J. M., and BOGERT, L. J.: The uric acid content of maternal and fetal blood, *J. Biol. Chem.* 32: 63, 1917.
2. POMMERENKE, W. T.: Placental interchange. I. On the concentration of certain nitrogenous substances in the blood, before and after passing the placenta, *J. Clin. Investigation* 15: 485, 1936.
3. HELLMUTH, K.: Beiträge zur Biologie des Neugeborenen. I. Mitteilung, *Arch. f. Gynäk.* 123: 57, 1924-25.
4. NAESLUND, J., Untersuchungen über den Übergang N-haltiger Stoffe vom Fötus auf die Mutter, *Acta obst. et gynec. Scandinav.* 11: 293, 1931.
5. SLEMONS, J. M.: The nutrition of the fetus, *Am. J. Obst.* 80: 194, 1919.
6. LICHTENSTEIN, A.: Untersuchungen am Nabelschnurblut bei Frühgeborenen und ausgetragenen Kindern mit besonderer Berücksichtigung der Aminosäuren, *Ztschr. f. Kinderh.* 51: 748, 1931.
7. MICHEL, C.: Recherches sur la nutrition normale du nouveau-né, Échanges nutritifs azotés et salins, *L'Obstetrique* 1: 140, 1896.
8. LANGSTEIN, L., and NIEMANN, A.: Ein Beitrag zur Kenntnis der Stoffwechselforgänge in den ersten vierzehn Lebenstagen normaler und frühgeborener Säuglinge, *Jahrb. f. Kinderh.* 71: 604, 1910.
9. BIRK, W.: Untersuchungen über den Stoffwechsel des Neugeborenen Kindes, Leipzig, Barth, 1912.
10. VON PFAUNDLER, M.: Physiologie, Ernährung, und Pflege des Neugeborenen, einschliesslich des Lebensschwachen; in *Handbuch der Geburtshilfe*, Vol. 1, Edited by A. Döderlein, München, J. F. Bergmann, 1924.
11. SCHLOSS, O. M., and CRAWFORD, J. L.: The metabolism of nitrogen, phosphorus and the purin substances in the new-born . . . *Am. J. Dis. Child.* 1: 203, 1911.
12. GORDON, H. H., LEVINE, S. Z., WHEATLEY, M. A., and MARPLES, E.: Respiratory metabolism in infancy and in childhood; the nitrogen metabolism in premature infants—comparative studies of human milk and cow's milk, *Am. J. Dis. Child.* 54: 1030, 1937.
13. LEVINE, S. Z., and GORDON, H. H.: Physiologic handicaps of premature infant; their pathogenesis, *Am. J. Dis. Child.* 64: 274, 1942.
14. HOEFFEL, G. N., and MORIARTY, M. E.: Amino-acid content of blood of infants and children, *Am. J. Dis. Child.* 27: 64, 1924.
15. SHERMAN, D. H., PUCHER, G. W., and LOHNES, H. R.: Blood chemistry of the new-born, *Am. J. Dis. Child.* 30: 496, 1925.
16. SIMON, S.: Zur Stickstoffverteilung im Urin des Neugeborenen, *Ztschr. f. Kinderh.* 2: 1, 1911.
17. VON REUSS, A. R.: *The Diseases of the Newborn*. London, John Bale Sons & Danielsson, 1920.
18. CZERNY, A., and KELLER, A.: *Des Kindes Ernährung, Ernährungsstörungen und Ernährungs-*

- therapie. 2 Aufl. Bd. 1 & 2, Leipzig, F. Deuticke, 1925-28.
19. (a) ORGLER, A.: Der Eiweissstoffwechsel des Säuglings, *Ergebn. d. inn. Med.* u. *Kinderh.* 2: 464, 1908.
 - (b) ORGLER, A.: Beiträge zur Lehre vom Stickstoffwechsel im Säuglingsalter, *Monatsch. f. Kinderh.* 7: 135, 1908.
 20. SCHLOSSMANN, A.: Über Menge, Art und Bedeutung des Phosphors in der Milch und über einige Schicksale desselben im Säuglingsorganismus, *Arch. f. Kinderh.* 40: 1, 1904.
 21. RUBNER, M., and LANGSTEIN, L.: Energie und Stoffwechsel zweier frühgeborener Säuglinge, *Arch. f. Physiol.* 39: 39, 1915.
 22. HAMILTON, B.: The calcium and phosphorus metabolism of prematurely born infants, *Acta paediat.* 2: 1, 1922-23.
 23. HAMILTON, B., and MORIARTY, M.: Composition of growth in infancy; I, a premature infant, *Am. J. Dis. Child.* 37: 1169, 1929.
 24. JOHN, F.: Über den Eiweissansatz bei Frühgeburten, *Ztschr. f. Kinderh.* 51: 794, 1931.
 25. BÁLINT, A., and STRANSKY, E.: Reststickstoffstudien an Neugeborenen, gleichzeitig ein Beitrag zur Frage des Harnsäureinfarktes, *Jahrb. f. Kinderh.* 93: 210, 1920.
 26. SEDGWICK, J. P., and ZIEGLER, M. R.: The nitrogenous and sugar content of the blood of the newborn, *Am. J. Dis. Child.* 19: 429, 1920.
 27. LUCAS, W. P., DEARING, B. F., and others: Blood studies in the newborn. . . . *Am. J. Dis. Child.* 22: 525, 1921.
 28. SALMI, T.: Untersuchungen über den Blutdruck und den Reststickstoff des Blutes beim Neugeborenen, mit besonderer Berücksichtigung der Kinder von Nierengestosemüttern, *Acta paediat.* 18: 92, 1935.
 29. SCHIFF, E.: Beiträge zur quantitativ-chemischen Zusammensetzung des im Laufe der ersten Lebenstage entleerten Harnes, *Jahrb. f. Kinderh.* 35: 21, 1893.
 30. GAMBLE, J. L., and GOLDSCHMIDT, S.: Study of creatinuria in infants. I. Relation of creatinuria to acidosis . . . *J. Biol. Chem.* 40: 199, 1919. II. Relation of protein intake to urinary creatine. *Ibid.*, 215.
 31. MARPLES, E., and LEVINE, S. Z.: Creatinuria of infancy and childhood . . . *Am. J. Dis. Child.* 51: 30, 1936.
 32. AMBERG, S., and MORRILL, W. P.: On the excretion of creatinin in the newborn infant. *J. Biol. Chem.* 3: 311, 1907.
 33. ROSE, W. C.: Excretion of creatin in infancy and childhood, *J. Biol. Chem.* 10: 265, 1911-12.
 34. PAFFRATH, H., and OHM, W.: Zur Frage der Kreatinurie des Frühgeborenen, *Ztschr. f. Kinderh.* 54: 377, 1933.
 35. WRIGHT, SAMSON: *Applied Physiology*, 7th Ed. New York, Oxford University Press, 1940.
 36. CAMERER, W. L.: Stoffwechsel und Ernährung im ersten Lebensjahr, in Pfaundler and Schlossman: *Handbuch der Kinderheilkunde*, Leipzig, Vogel, 1906.
 37. MARPLES, E.: Creatinuria in infancy and in childhood: creatinuria of premature infants, *Am. J. Dis. Child.* 64: 996, 1942.
 38. SEDGWICK, J. P., and KINGSBURY, F. B.: The uric acid content of the blood in the new-born, *Am. J. Dis. Child.* 14: 98, 1917.
 39. PETERS, J. P., and VAN SLYKE, D. D.: *Quantitative Clinical*

- Chemistry; Volume 1—Interpretations. Baltimore, Williams & Wilkins, 1931–32.
40. BIRK, W.: Der Stoffwechsel des Kindes während der ersten Lebensstage, *Monatschr. f. Kinderh.* 10: 1, 1912.
 41. REUSING, H.: Beiträge zur Physiologie der Neugeborenen, *Ztschr. f. Geburtsh. u. Gynäk.* 33: 36, 1895.
 42. REITSCHEL, H.: Zur Entstehung des Harnsäureinfarktes beim Neugeborenen, *Monatschr. f. Kinderh.* 22: 241, 1921.
 43. BERGER, G.: Über den Harnsäure- und Gallenfarbstoffgehalt des Nabelschnurblutes, *Ztschr. f. Kinderh.* 54: 196, 1933.
 44. WINDLE, W. F.: *Physiology of the Fetus: Origin and Extent of Function in Prenatal Life*, Philadelphia, W. B. Saunders, 1940.
 45. DARROW, D. C., and CARY, M. K.: Serum albumin and globulin of newborn, premature and normal infants, *J. Pediat.* 3: 573, 1933.
 46. RAPOPORT, M., RUBIN, M. I., and CHAFFEE, D.: Fractionation of serum and plasma proteins by salt precipitation in infants and children . . . *J. Clin. Investigation* 22: 487, 1943.
 47. RUSZ, E.: Die physiologischen Schwankungen der Refraktion und Viskosität des Säuglingsblutes, *Monatschr. f. Kinderh.* 10: 360, 1912.
 48. UTHEIM, K.: A study of the blood and its circulation in normal infants and in infants suffering from chronic nutritional disturbances, *Am. J. Dis. Child.* 20: 366, 1920.
 49. BAKWIN, H.: Dehydration in newborns, *Am. J. Dis. Child.* 24: 497, 1922.
 50. RAY, H. H., and PHATAK, N. M.: Diffusible blood serum calcium in normal new-born infants, *Am. J. Dis. Child.* 40: 549, 1930.
 51. MARPLES, E., and LIPPARD, V. W.: Acid-base balance of new-born infants. II. Consideration of the low alkaline reserve of normal new-born infants, *Am. J. Dis. Child.* 44: 31, 1932.
 52. ANDERSCH, M., and OBERST, F. W.: Filterable serum calcium in late pregnant and parturient women, and in the newborn, *J. Clin. Investigation* 15: 131, 1936.
 53. DENZER, B. S., REINER, M., and WEINER, S. B.: Serum calcium in newborn, *Am. J. Dis. Child.* 57: 809, 1939.
 54. YOUNG, W. F., HALLUM, J. L., and McCANCE, R. A.: Secretion of urine by premature infants, *Arch. Dis. Childhood* 16: 243, 1941.
 55. LEWIS, J. H., and WELLS, H. G.: The function of the colostrum, *J. A. M. A.* 78: 863, 1922.
 56. BOYD, G. L.: The value of colostrum to the newborn, *Canad. M. A. J.* 12: 724, 1922.
 57. ACHARD, C., BARIÉTY, M., and CODOUNIS, A.: L'Équilibre protéique du sérum comparé dans le sang de la mère et le sang du cordon ombilical, *Compt. rend. Soc. de biol.* 102: 984, 1930.
 58. HICKMANS, E. M., FINCH, E., and TONKS, E.: Plasma protein values in infants, *Arch. Dis. Childhood* 18: 96, 1943.
 59. HOLMAN, A., and MATHIEU, A.: Blood chemistry studies of normal newborn infants; blood sugar and alkali reserve estimations, *Am. J. Obst. & Gynec.* 27: 95, 1934.
 60. ARON, M.: La glycémie chez l'embryon, *Compt. rend. Soc. de biol.* 89: 187, 1923.
 61. BRITTON, S. W.: Maternal and

- fetal blood sugar changes under various experimental conditions. *Am. J. Physiol.* 95: 178, 1930.
62. NAESLUND, J.: Investigations into transit of reducing substances from mother to foetus in alimentary hyperglycaemia, *Acta Obst. et Gynec. Scandinav.* 7: 25, 1928.
 63. DAHL, P.: Maternal and fetal blood sugar under varying experimental conditions, *Acta Obst. et Gynec. Scandinav.* 7: 363, 1928.
 64. CLOGNE, R.: Dosage du glycogène dans le foie du foetus et dans le placenta, *Gyn. et Obstetrique* 10: 23, 1924.
 65. TRAINA RAO, G.: Sul quantitativo di glicogeno della placenta e del fegato fetale in casi normali ed in casi patologici, *Riv. ital. di ginec.* 15: 351, 1933.
 66. MORRIS, W. H.: Obstetrical significance of the blood-sugar with special reference to the placental interchange, *Bull. Johns Hopkins Hosp.* 28: 140, 1917.
 67. GREENWALD, H. M., and PENNELL, S.: Carbohydrate metabolism of the normal new-born infant . . . *Am. J. Dis. Child.* 39: 281, 1930.
 68. SHRETTER, G., and NEVINNY, H.: Der Blutzucker in den ersten Lebenstagen, *Ztschr. f. Geburtsh. u. Gynäk.* 98: 258, 1930.
 69. WINTER, E. W.: Studien über den Kohlehydratstoffwechsel. . . *Arch f. Gynäk.* 1: 154-354, 1933.
 70. COBLINER, S., Blutzuckeruntersuchungen bei Säuglingen, *Ztschr. f. Kinderh.* 1: 207, 1910.
 71. HARTMANN, A. F., and JAUNDON, J. C.: Hypoglycemia, *J. Pediat.* 11: 1, 1937.
 72. KETTERINGHAM, R. C., and AUSTIN, B. R., Blood sugar during labor, at delivery and postpartum, with observations on newborns, *Am. J. M. Sc.* 195: 318, 1938.
 73. MCKITTRICK, J. B.: Serial blood sugar determinations in normal newborn infants, *J. Pediat.* 16: 151, 1940.
 74. See Chapter 3, References 9-16.
 75. HELLER, F.: Der Blutzuckergehalt bei Neugeborenen und frühgeborenen Kindern, *Ztschr. f. Kinderh.* 13: 129, 1915.
 76. HAASS, F.: Beobachtungen über die Blutzuckerregulation bei Frühgeborenen, *Ztschr. f. Kinderh.* 51: 400, 1931.
 77. VAN CREVELD, S.: Carbohydrate metabolism of premature infants. I. The blood sugar during fasting, *Am. J. Dis. Child.* 38: 912, 1929.
 78. SVENSGAARD, E.: Blood sugar in normal and sick children, with special reference to coeliac disease, *Acta paediat. (supp. 4)* 12: 1, 1931.
 79. KETTERINGHAM, R. C.: Dextrose tolerance tests of the newborn, *Am. J. Dis. Child.* 59: 542, 1940.
 80. BENTIVOGLIO, G. C.: Nuovi criteri clinici intorno al comportamento digestivo e all'uso delle sostanze amidacee nei primi mesi di vita, *Riv. di clin. pediat.* 26: 96, 1928.
 81. IBRAHIM, J.: Die Doppelzuckerfermente Laktase, Maltase und Invertin beim Neugeborenen und Embryo, *Ztschr. f. phys. Chemie.* 66: 19, 1910.
 82. NOTHMANN, H.: Laktase und Zuckerausscheidung in frühgeborenen Säuglingen, *Monatschr. f. Kinderh.* 8: 377, 1909.
 83. VON REUSS, A.; and ZARFL, M.: Chronische Laktosurie bei einem darmgesunden Brustkinde, *Wien med. Wehnschr.* 65: 854, 1915.
 84. GROSZ, J.: Beobachtungen über

- Glycosurie im Säuglingsalter, *Jahrb. f. Kinderh.* 34: 83, 1892.
85. HOENIGER, E.: Über die ephe-
mere traumatische Glykosurie
bei Neugeborenen, *Deutsche,
med. Wehnschr.* 37: 500, 1911.
 86. LINDIG, P.: Zur Glykosurie des
Neugeborenen, *Klin. Wehnschr.*
1: 995, 1922.
 87. LEVINE, S. Z., and GORDON,
H. H.: Physiologic handicaps of
premature infant; clinical appli-
cations, *Am. J. Dis. Child.* 64:
297, 1942.
 88. MORSE, J. L., and TALBOT, F. B.:
*Diseases of Nutrition and Infant
Feeding.* New York, Macmillan,
1915.
 89. PETERS, J. P.: A new frame for
metabolism, *Yale J. Biol. &
Med.* 13: 739, 1941.
 90. WACKER, L., and BECK, K. F.:
Untersuchungen über den Fett-
und Cholesterinstoffwechsel
beim Säugling, *Ztschr. f.
Kinderh.* 29: 331, 1921.
 91. HOLT, L. E.: A study of the fat
metabolism of infants and young
children. I. Fat in the stools of
breast-fed infants, *Am. J. Dis.
Child.* 17: 241, 1919.
 92. HOLT, L. E., JR., TIDWELL,
H. C., and others: Studies in fat
metabolism. I. Fat absorption in
normal infants, *J. Pediat.* 6: 427,
1935.
 93. TIDWELL, H. C., HOLT, L. E.,
JR., FARROW, H. L., and NEALE,
S.: Studies in fat metabolism. II.
Fat absorption in premature in-
fants and twins, *J. Pediat.* 6:
481, 1935.
 94. GORDON, H. H., and McNA-
MARA, H.: Fat excretion of pre-
mature infants; effect on fecal
fat of decreasing fat intake, *Am.
J. Dis. Child.* 62: 328, 1941.
 95. TOBLER, and BOGEN, H.: Über
die Dauer der Magenverdauung
der Milch und ihre Beinflussung
durch Verschiedene Faktoren,
Monatschr. f. Kinderh. 7: 12,
1908.
 96. IVY, A. C.: Physiology of the
gastrointestinal tract. Chapter
20, Vol. I, *Practice of Pediatrics*,
ed. by Joseph Brennemann, Hag-
erstown, W. F. Prior, 1942.
 97. BOYD, E. M., and WILSON,
K. M.: Exchange of lipids in um-
bilical circulation at birth, *J.
Clin. Investigation* 14: 7, 1935.
 98. IMRIE, C. G., and GRAHAM, S. G.:
The fat content of embryonic
livers, *J. Biol. Chem.* 44: 243,
1920.
 99. SLEMONS, J. M., and STANDER,
H. J.: The lipoids of maternal
and fetal blood at the conclusion
of labor, *Bull. Johns Hopkins
Hosp.* 34: 7, 1923.
 100. HELLMUTH, K.: Beiträge zur
Biologie des Neugeborenen. II.
Mitteilung, *Arch. f. Gynäk.* 127:
293, 1925-26.
 101. ROSENBLUM, D.: Cholesterol of
maternal and fetal blood at the
conclusion of pregnancy, *Proc.
Soc. Exper. Biol. & Med.* 32:
908, 1934-35.
 102. GENTILI, A.: Il ricambio dei
lipidi nell'infanzia in condizioni
normali e patologiche, *Arch. ital.
di pediat. e puericolt.* 3: 135,
1935.
 103. BOYD, E. M.: Lipid composition
of blood in new-born infants,
Am. J. Dis. Child. 52: 1319,
1936.
 104. SENN, M. J. E., and McNAMARA,
H.: Lipids of blood plasma in
neonatal period, *Am. J. Dis.
Child.* 53: 445, 1937.
 105. SPERRY, W. M.: Cholesterol of
the blood plasma in the neonatal
period, *Am. J. Dis. Child.* 51:
84, 1936.

Chapter X

THE ASSIMILATION AND METABOLISM OF MINERALS AND VITAMINS

Section 1 . . . Mineral Metabolism

Section 2 . . . Vitamin Metabolism

Section 3 . . . Clinical Summary

MINERAL METABOLISM

IN THE LARGE AND rapidly growing field of mineral metabolism, the special relationships of the pregnant and lactating mother to the developing fetus and the growing infant have been intensively cultivated. However, in the long chronological sweep of development, which begins with the embryo and culminates in the fully-grown adult, the space occupied by the immediately post-natal period is proportionately very small. Perhaps it has been further minimized since it represents a brief period of relative hesitation dividing two definite epochs of advancing general and mineral growth. The almost irresistible demands of fetal growth have been studied with special reference to the obligations under which maternal stocks and supplies are placed; the more modifiable developments of infancy and childhood have been investigated with particular regard to the effects upon them of dietary factors. Attention to the newborn period has however mainly been focused upon the concentrations of minerals in the blood, and their connections with possible symptoms of disease. Only calcium, phosphorus, and iron will be discussed in this chapter. The reader who wishes further information on the entire subject of mineral metabolism is referred to Shohl's recent book¹ and to the review by Stearns² which appeared in the same year.

Calcium is traditionally considered together with phosphorus although their common ground in the body is practically restricted to that of bone formation. While phosphorus has many other physiologic aspects, Stearns says that "as over 98 per cent of body calcium is found in bone, a discussion of calcium metabolism is a discussion of skeletal growth and mineralization."² Calcium (and bone) accumulates in the developing fetus as shown in Figure 30, reproduced through the courtesy of Dr. Stearns. It should be

noted that the ordinates are percentages of body weight; were they actual grams of calcium the rising line of calcium acquisition would be a curve, swinging rapidly upward as fetal growth accelerates in the last part of gestation. From curves of this sort as prepared by other authors^{3,4} total calcium has been shown to increase about as follows:

Period of Gestation	Total Fetal Calcium	Increase
Before 4 lunar months	1 gram	
4 to 6 lunar months	3.7 grams	2.7 grams
6 to 8 lunar months	8.9 grams	5.2 grams
8 to 10 lunar months	21.0 grams	12.1 grams

Although these are averages from data which show a surprising scatter at the time of birth³ it is obvious that more than half the acquisition occurs during the last fifth of gestation. Whether the process is directly dependent upon the mother's diet and health is apparently a relative matter, for while maternal states of severe hypocalcemia may be reflected in the birth of a poorly mineralized

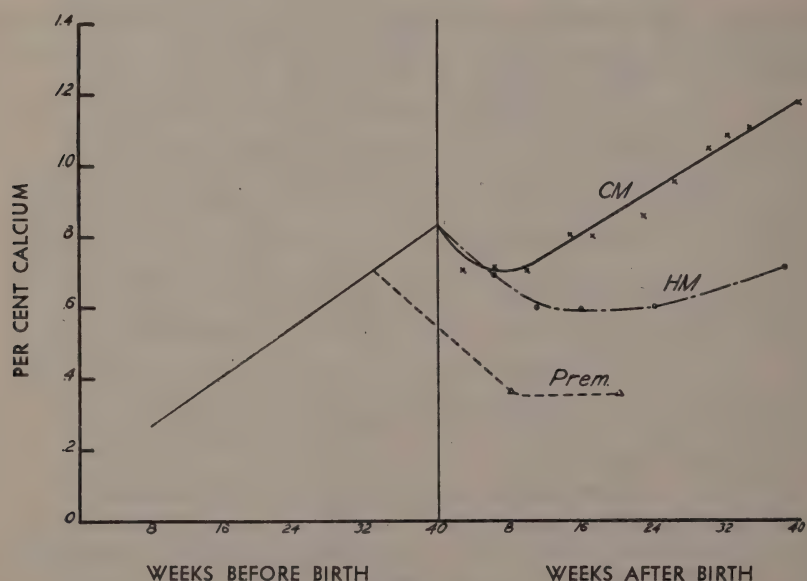


FIGURE 30

Percentage of body weight represented by calcium before and after human birth. C. M. and H. M. represent determinations from full-term infants fed human and cow's milk respectively. Prem. indicates the status of premature infants fed human milk. (Stearns, *Physiol. Rev.*, 19: 415, 1939.)

infant, milder failings in maternal intake seem to allow normal storage by the fetus.^{2,4-6} By the time of normal birth the skeleton has acquired decidedly more calcium than is available to the infant born prematurely, but from Figure 30 it is clear that extra-uterine life, at whatever stage it begins, imposes conditions quite different from those under which calcium acquisition relative to body mass was previously progressing *in utero*. Calcium equilibrium does not necessarily become negative but temporarily ceases to be as definitely positive as before. Questions of equilibrium between intake and outgo have led to attempted mathematical answers from balance experiments in the newborn period.⁷⁻⁹ Concerning the resultant data, it is probably as well merely to state that positive calcium balances have been demonstrated very soon after birth, but as Shohl¹ says, "Owing to the complicated problems involved and doubt as to the significance of very small positive and negative balances, none of the data is here reproduced." Calcium is removed from the body primarily by the bowel, which takes off not only the unabsorbed dietary residue but also some actual excretion through the intestinal wall. A daily calcium intake of 100 to 150 mgm. seems an almost essential requisite to cover daily fecal removal; ingestion must be above this level for any retention to occur. A normally insignificant portion is also excreted by the kidney. The ingestion of increasing amounts of calcium leads to a larger fecal loss but also to rather surprising degrees of increased retention. Thus the *prime* factor governing the degree of retention is not the infant's powers of absorption, which are very flexible, nor the state of its digestion, vitamin D economy, or relative intakes of other minerals—important though all these may be—but the amount of calcium in the diet. And in newborn life this is unavoidably limited by the total amount of food that can be ingested as well as by the calcium concentration in that food.

Cow's milk contains from three to four times as much calcium as human milk. Therefore, while an infant a week old would receive in 18 ounces of breast milk about 180 mgm. calcium per day, in the same amount of standard diluted cow's milk formula it could receive about 430 mgm. Although calcium is proportionately somewhat better retained from a diet of human milk than one of cow's milk with added vitamin D, the widely different mineral content of the two feedings will nevertheless be reflected by a difference in calcium retention such as separates the line marked C.M. and H.M. in Figure 30. The line representing human milk descends further after birth and rises from its low point more gradually. Swanson's¹⁰ data are reproduced for their instructive indications of the mathe-

matical level of retention performance; although the periods studied were not all within strictly neonatal limits, there is no reason to doubt that the same general phenomena occur soon after birth.

Not only will the infant derive a higher mineral intake from cow's milk, but if extra calcium be added to such a diet a still greater retention may be attained, and this without a proportionate retention of water, so that the minerals are said to be added "dry" to the body.^{11,12} This "supermineralization" has never been shown to harm the organism; the difficulty is to know whether it

TABLE 37
EFFECT OF DIET UPON MINERAL RETENTION

Substance	Breast Milk		Cow's Milk	
	Without Cod Liver Oil	With Cod Liver Oil	Without Cod Liver Oil	With Cod Liver Oil
Calcium	0.20	3.58	5.74	14.56
Phosphorus	1.46	2.68	5.35	8.05
Sodium	2.53	2.24	4.87	5.62
Potassium	2.50	2.42	4.56	5.19
Magnesium	0.40	0.74	1.64	1.26
Chlorine	2.02	2.00	4.84	6.08
Sulfur	1.12	0.68	1.00	0.08
Nitrogen	40.40	36.70	66.66	65.90

(Data re-arranged by Shohl¹ from Swanson¹⁰ in milliequivalents retained per day.

Subject at beginning of observations aged 2 weeks; at end, 6 months.)

offers any advantages. For although avoidance of rickets or other evidence of deficiency is obviously to be desired, there is doubt as to where a line should be drawn above which mineral retention is not merely an experimental *tour de force*.

The performance of the prematurely born infant is a strikingly poor one, as shown in Figure 30, and the general reasons need not be elaborated. That no essential inadequacy of the organism (beyond its limited storage period *in utero*) is to be blamed is evident from two studies which have shown premature infants to be capable of about as good calcium retention as full term infants, provided the requirements of intake were satisfactorily met.^{13,14} It is most interesting that the premature babies studied by Paffrath and Massart¹⁴ achieved a real "supermineralization" on a high calcium intake, even though no extra vitamin D appears to have been

given them. The protocols of these authors include records showing even tenfold increases in calcium retention by premature infants as soon as the intake of that material was elevated by feeding cow's milk mixtures. Again, such retentions were more or less "dry" ones, since the minerals were retained without proportionately increased additions of water to the tissues.

One cannot help being impressed by the implications of the material just presented. The infant, whether delivered at or before normal term, possesses astonishing flexibility in utilization of the calcium of his diet. On a comparatively low intake he will retain but little; on a larger intake he is capable of retaining and depositing an amount many times as great as before this was supplied. So wide are the boundaries of this ability that no upper limit has been fixed, but so indifferent is the infant's skeleton to the resulting dep-

TABLE 38

SERUM CALCIUM AND PHOSPHORUS OF NEWBORN INFANTS¹⁵

Source	Calcium			Phosphorus		
	Number of Measurements	Average (mgm./100 cc.)	Range	Number of Measurement	Average (mgm./100 cc.)	Range
Literature reviewed by Todd, Chuinard, and Wood	745 cord	10.85	8.3-14.4	619 cord	4.26	1.9-13.3
	87 fontanel	12.08	9.9-12.5	26 font.	6.31	4.4-11.3
	832 total	10.97	8.3-14.4	645	4.30	1.9-13.3
Todd, et al.; own. results*	121 cord	11.27	7.3-16.9	121 cord	5.55	4.2-8.0
	630 fontanel #1	9.93	7.2-12.3	548 font. #1	6.08	3.7-8.6
	573 fontanel #2	10.45	7.5-13.9	530 font. #2	5.93	3.5-7.6

* Fontanel #1 specimens secured before the third day of life.

Fontanel #2 specimens secured from fourth to seventh day of life.

ositions that no evidence has emerged by which one can decide upon an optimum range to be aimed at or a harmful level not to be exceeded.

Numerous measurements of the calcium concentration in the blood of the newborn infant have been published. Todd and his colleagues¹⁵ list twenty separate studies from the literature and add a monumental collection of more than a thousand determinations made by themselves; while one more set of useful data was presented by Denzer and others.¹⁶ Why so much effort has been expended upon the problem is a little curious, for there is quite good agreement in almost all the results (the body's regulatory powers being what they are) and, moreover, one suspects that variations in total serum calcium are not particularly helpful data for solving the problems of neonatal calcium economy, except as they relate to the rather unusual appearance of tetany at this time of life. Table 38

is taken from Todd's paper and is in general agreement with Denzer's results.

Several investigators include a figure for the maternal serum calcium concentration at birth, which, with one exception,¹⁷ has been found to be below the fetal level by at least one mgm.^{6,18-22} There is no agreement among investigators as to whether the level of calcium on one side of the placenta is related to that on the other. Certainly there is no striking correspondence. Prematurely born infants have shown the same general concentrations of calcium in the cord blood as have infants born at term.²¹

Calcium is known to exist in two general physical forms in the blood: the one a diffusible or filterable fraction (probably of importance in the production of tetany) composed almost entirely of ionized calcium, and the other a more inert non-diffusible fraction consisting of calcium bound to protein. Ray and Phatak²² and Andersch and Oberst²³ have independently investigated the filterable or diffusible calcium of neonatal serum and have both found the same average value for it of 5.3 mgm. per cent, although the material used by the former workers was obtained from infants between 5 and 22 days old whereas that examined by the latter was cord blood obtained at birth. A slightly higher value of 5.9 was found in cord blood by Bockleman and Bock²⁴ in earlier studies. Andersch and Oberst²³ checked their actual determinations against calculated values for ionized calcium arrived at by the McLean and Hastings method²⁵ from measurements of total calcium and serum protein. In maternal blood the agreement was close, as should be the case: in cord blood it was not close, the value predicted by calculation being considerably above that actually obtained by measurement. "Apparently, there are other factors which must be considered in using the calculations proposed by McLean and Hastings, or there is some characteristic of fetal blood which disturbs the equation they have developed."²³ Indeed the calculated figure of 6.4 mgm. per cent was above the actually measured one by as much as 1.1 mgm. per cent. This fact might be taken into account in applying data obtained only by calculation and not by direct measurement to a tentative diagnosis of tetany in a recently born infant.

However this difference is to be explained, a brief summary may be useful here to conclude the discussion of this subject. Although skeletal calcium is relatively diminished in the premature as compared with the full term infant at birth, calcium may be deposited in the bones of either type of infant to a widely varying degree dependent upon the food and vitamin D intake. The total calcium of the blood

is about one milligram per cent above that in the mother's blood at either premature or full term birth. Thereafter it undergoes a definite though slight increase until about the third day of life. The diffusible or ionized calcium of the fetal and maternal blood at birth are at approximately the same level, actually a lower one than is arrived at by calculations involving the blood protein of the newborn subject.

Phosphorus exists in the body in both organic and inorganic combinations, so that the possibilities for changes in its various partitions are more complex than is the case with calcium. The inorganic phosphorus of the blood is a numerically much smaller fraction than is that entering into the organic combinations which are mainly carried in the cells. Facts concerning these organic phosphorus compounds are just beginning to emerge; little is known at present about their adjustment in newborn life.^{26,27} In the following discussion quantitative data will therefore relate only to the inorganic phosphate of the serum or plasma, which is, indeed, the portion usually referred to when unspecified figures of "blood phosphorus" are quoted. In general, the increase of phosphorus in the fetal body follows a curve like that for calcium, rising (though less steeply) during the last months of gestation. The fetus and newborn infant of a well-nourished mother whose mineral and vitamin D intakes have been satisfactory will possess more body phosphorus than will the offspring of a poorly nourished woman.^{2,28} After birth the storage of phosphorus continues to depend upon the amount available in the infant's diet and upon the stimulus to absorption and deposition offered by added vitamin D, as is shown in Table 37 above. Again there is no evidence that phosphorus retention to a certain definite mathematical level is an essential for optimal growth, nor that an increased acquisition of phosphorus above that level does harm to the infant.

It is an established fact that the inorganic phosphorus of the infant's blood at birth is, like the calcium, above the maternal blood concentration,^{2,15} with a normal range of some 4 to 8 mgm. per cent in serum from the cord. The average of Todd's series was 5.55 (Table 38). From this and other work²⁹ it appears that whereas the calcium of the blood declines during the first few days after birth, the phosphorus rises, so that very little change takes place in the product of the two figures. It is obvious that the post-natal variations in these minerals are, although under reasonably accurate control, nevertheless in a direction which would lead toward tetany, and indeed tetany has been more common in the neonatal period than has rickets. The post-natal fall in serum calcium ap-

pears to be checked before any large amount of dietary calcium might be supposed to have an effect in overcoming it, so that certain authors, notably Bakwin,³⁰ have postulated a relative hypoparathyroidism in the first 48 hours after birth. By some natural readjustment this glandular regulation seems to be returned to a normal activity thereafter, and the serum calcium swings upward again at about the third day. Bakwin has called attention to the large amount of phosphorus furnished by cow's milk as compared to human milk. Since he has brought experimental evidence to indicate that excess dietary phosphorus depresses serum calcium, he suggests that cow's milk feedings given during the neonatal period may increase the tendency of a normally occurring transient hypoparathyroidism to produce tetany. Other authors¹⁶ have taken issue with this theory, but it must be admitted that a very definite and not otherwise explained mechanism must obviously intercede to reverse the falling trend of neonatal blood calcium before a tetanic range is reached.

Since, according to Eliot and Park,³¹ "it seems probable that phosphatase is concerned in some vital way with the cellular activities of bone and the phosphate and hence the calcium metabolism of the body," it may be pertinent to include here the quantitative data upon that enzyme in normal neonatal life. Although Stearns and Warweg's measurements²⁷ are expressed in Kay units and presented graphically rather than numerically, while Barnes and Munks' figures³² are in Bodansky units, the purport of both is roughly similar. Serum or plasma phosphatase activity is comparatively low at birth and rises to much higher levels in the first few

Age	Number of Cases	Mean Bodansky Units per 100 cc.	Standard Deviation
0 - 3 days	45	7.1	2.66
3 - 15 days	23	8.9	2.39
2 - 6 weeks	33	10.4	3.05
1½ - 2½ months	30	11.9	3.01
2½ - 3½ months	28	12.1	2.52
4½ - 5½ months	34	13.0	2.92
5½ - 6½ months	27	11.4	2.88

weeks. Barnes and Munks give the figures listed for serum phosphatase. The ascent shown by the data of Stearns and Warweg was a still sharper one, so that values two or three times as high as the birth levels were attained in one or two months. The general type of change is one which might well accompany an increasingly active calcification. Why phosphatase activity should be so low at

birth, when calcification ought also to be proceeding energetically, cannot be stated. Locally, in bone itself, phosphatase activity is said to be greater just before birth than at any time of life.³³ This was determined from the bones of rabbits; whether it would also be true of the human organism is an interesting question.

The other mineral deserving consideration here is **iron**. Like those mentioned above, it is added to the fetal body in amounts which to some extent depend upon the maternal intake. Just how it crosses the placenta is not yet clear, but some light has been thrown upon the mode of transfer by tracing the fate of radio-active iron preparations fed to women shortly before delivery. Pommerenke and his colleagues, who carried out this study,³⁴ learned that the iron reached the fetal circulation in appreciable amounts within 40 minutes after its ingestion by the mother, a rapidity which suggested to them that the plasma was the vehicle used, rather than the red blood cells. In the latter case the cells would have to absorb the iron, be carried to the placenta, broken down there and thus release it for the fetus. In the bodies of aborted fetuses the identifiable iron was widely disseminated, mostly concentrated in the red blood cells and secondarily in the liver.

Utheim-Toverud³⁵ has found the average amount of iron per 100 grams of liver in premature infants of 26 to 36 weeks gestation to be 168 mgm., whereas the figure for newborn subjects at full term was 200 mgm. Iob and Swanson³⁶ have shown the same tendency for fetal liver to contain more iron as gestation proceeds, and for the total fetus to contain more iron per kilogram of body weight at its full growth than earlier in its development. However, they have also called attention to the important fact that, per kilo of fat-free, water-free body substance, the concentration of fetal iron remains essentially the same during fetal growth. In other words the "increased storage" of iron during intra-uterine development is probably less an actual than an apparent phenomenon, and is due in some part to the physiological removal of water from the body during this period.

It should be noted that there is a great deal less of iron than of some other minerals in the body, the amounts in the case of calcium and of iron differing as about 25 to 1. Estimations of this relatively small component of iron in tissues and fluids are not so easily nor so often performed as other mineral measurements. As a result of this and of other factors, there is a tendency to think of iron in the more easily measurable terms of red blood cells and hemoglobin. But the infant has rather specially ordained amounts of erythrocytes and hemoglobin at hand when it is born, and the production of these is thereafter regulated by more factors than merely that of

available iron. Therefore, while it would be impractical to discuss changes in iron metabolism during the first weeks of life without frequent attention to the state of the blood, it should not be assumed that this state is simply the expression of the body's stores of iron.

At birth the blood has been shown to have an amount of hemoglobin beyond the requirements of its new environment; then, particularly from the third to the ninth week of life, there occurs a fall in hemoglobin and red blood cells. In premature infants who start extra-uterine life with less iron than do full-term ones, and who grow more rapidly, these changes are usually more marked and last for a longer time. According to Stearns, all infants during these weeks of increasing "physiological anemia" tend to show an actual loss of some iron from the body, a loss which she says should give little concern.^{2,37} Nevertheless, much interest has centered upon the quantity of iron which is supplied by the usual foods or perhaps should be made available by supplemental drugs as a means of relieving or forestalling this development. This, in turn, brings up more fundamental questions as to the neonatal subject's ability to assimilate usual or excess amounts of iron so supplied. Josephs,^{38,39} whose contributions should be consulted, has brought forward evidence to show that "about 0.17 mg. of iron per kg. body weight per day must be ingested by the infant of less than three months to bring the intake and output into equilibrium, and that if less than this is given the tendency is toward a negative balance." But in another part of the same paper he also says that "infants from birth to three months show such wide variations in retention of iron that it seems best to disregard them from the discussion of this problem."³⁹

The latter statement limits the significance of the former; still it is of interest to calculate what may be expected of milk for the provision of 0.17 mgm. of iron per kilogram of the infant's weight. An infant of 4 kilograms (about 8 pounds 12 ounces) would require about 0.7 mgm. of iron daily. Milk varies greatly in iron content. Human milk, furnishing from 0.5 to 1.5 mgm. of iron per liter¹ might supply the requirement. Cow's milk, which contains about a third as much iron, would fall definitely short of the mark. With certain reservations, balance studies bear out the implication that the equilibrium will be more nearly a positive one, or at least a less negative one, if the young infant is nursed than if he is being fed from a bottle.^{37,40} But actually there has been no general acceptance of the idea that the normal depression of hemoglobin level which occurs especially in the second and third months of life can be pre-

vented by increasing the iron supplied (or even that retained) before and during those months.³⁸ Once it is well established, the period of "physiological anemia" may indeed be curtailed by the feeding of extra iron, and the more true anemia of prematurity may, by the same measure, be made less severe and more like that following full-term birth.

VITAMIN METABOLISM

Without regard for the alphabet, **vitamin D** will be considered before the other accessory food substances because it bears so definite a relationship to certain of the minerals just discussed. Because no methods of direct assay are available there is little direct information as to the fate of this substance in fetal or neonatal nutrition. By indirect measurements, Toverud and Ender⁴¹ found that the livers of a series of 45 newborn infants showed no demonstrable vitamin D whatever in most cases. Of the other subjects, those showing the largest quantities of vitamin D (and this not a very large amount) were delivered from mothers whose diets had included more eggs and milk than the average. Although the livers of some prematurely born subjects were included, there was no correlation between fetal age and the absence or presence of the vitamin.

Further evidence as to vitamin D economy in the newborn can only be sought from the early appearance of rickets and from measurements of the concentrations of minerals in the blood. Such testimony is, in a way, almost as unsatisfactory for drawing conclusions as to the body's dealing with vitamin D itself as are the evidences furnished by hemoglobin changes after birth for drawing conclusions as to fetal and neonatal iron absorption and retention. Some weeks or months are required for clinical and biochemical evidences of rickets to appear after the onset of vitamin deficiency. Moreover, it is difficult to tell from animal experiments whether a maternal diet rich in vitamin D actually increases the availability of the vitamin to the fetus and newborn, or merely places more maternal minerals at the fetal command, though there is evidence that something of the former sort may occur.⁴² For whatever reason, it is true that the offspring of experimental animals fed extra vitamin D are better supplied with calcium and phosphorus at birth than the offspring of control animals.^{42,43} Conversely, the earlier that human rickets is discovered after birth the more commonly has the diet of the mother been insufficient in minerals and vitamin D during pregnancy and lactation, so that such mothers themselves often have osteomalacia. Even under such circumstances clinical

rickets is an extreme rarity at birth and indeed until the first month is past.^{31,44} Nevertheless it is probable that a rachitogenic status is often established during the first month or even the first week, although the effects of this take time to declare themselves clinically. Premature and twin infants are characteristically prone to develop rickets, the stage being set for this event by the combination of low fetal storage of minerals, the requirements of rapid growth, and, perhaps, the deficiencies of fat absorption from the bowel.³¹

The practical aspects of the subject merit consideration, particularly with regard to the anti-rachitic effectiveness or lack of effectiveness of human and of cow's milk diets in the newborn period. For the *prevention* of clinical rickets must often actually be the *therapy* of the incipient or "sub-clinical" process. It is apparent from Table 38 that cow's milk is superior to human milk in causing the deposition of calcium and phosphorus in the infant organism; indeed Benjamin, Gordon and Marples¹³ have brought forward evidence to show this to be the case even in premature infants. On the other hand, the widely substantiated fact is that rickets is less prone to occur in nursing babies than in those fed from the bottle, an observation that has led to hopeful but rather unsatisfactory attempts to discover a superiority in vitamin content or mineral inter-relationships in human milk.^{45,46} In neither human nor cow's milk have important quantities of vitamin D been found present, although both milks may be much enriched in that respect by increasing the maternal vitamin intake. It may be concluded that if a vitamin D supplement is given early either food will supply the minerals needed for bone growth (cow's milk furnishing more than human), but that if this supplement is neglected less potential harm will be done the nursing than the bottle-fed infant. The question then arises: if, on the other hand, vitamin D is given in this manner by the end of the first two or three weeks after birth, does an infant receiving the extra minerals of cow's milk have a clinically significant advantage over a nursing baby receiving the same supplement? There is nothing to suggest that this is so. In any case, full term infants probably should start to receive such a supplement to their daily diet at this time, and premature or otherwise small infants should certainly be given it. Since exposure to sunlight causes the deposition of vitamin D in the body some advantage may be taken of this natural source, particularly for infants born in the warmer months of the year.

Vitamin A studies can be based upon quantitative measurements. These have been made upon tissues such as the placenta,⁴⁷ fetal liver,^{41,47-49} and maternal, fetal and neonatal blood.^{47,49-53} De-

terminations have included both the vitamin itself and its carotenoid precursors. The general impression from these studies is one of wide variation in the infant's reserve supply of these factors at the time of birth, but of a rough parallelism between these fetal stores and the maternal diet during pregnancy. Storage in adults is known to take place particularly in the liver; therefore the fact that the livers of premature and full term fetuses contain quite large amounts of vitamin A is of some interest. In the study of 20 such livers made by Lewis and his associates in New York⁴⁹ the average amount (115 U.S.P. units per gram of liver) was more than twice that obtained in a similar study in Holland,⁴⁸ which in turn gave results somewhat higher than were obtained by Wendt in Munich⁴⁷ and very much above those obtained in the Norwegian investigation of Toverud and Ender.⁴¹ The different results from these various national groups suggest an important effect of the maternal diet.

A second finding of most investigators has been an inverse relationship between the amount of vitamin A storage per gram of liver and the gestational age of the fetus. On the average, and within a very wide range of measurements, the liver of the fetus at 3-5 months is twice as rich in vitamin A as at 6-10 months.⁴⁷ Although the growth in total liver mass tends to outweigh this discrepancy, it is something of a nutritional rarity to find a diminishing rather than an increasing storage of an important substance as birth approaches. Apparently the placenta itself contains no appreciable stock of vitamin A,⁴⁷ nor is the precursor carotene available in the liver at birth.⁴⁷ The umbilical vein blood of the fetus is richer in both precursor substance and actual vitamin A than is the umbilical artery blood, so that the addition to the fetal supply appears to arrive directly by this route.⁵¹ Nevertheless, the mechanism of transport across the placenta is certainly not a simple one, for large elevations in vitamin A or carotene produced experimentally in the blood of women nearing delivery are not productive of similar changes in the umbilical cord blood.⁵³

Although the blood appears to be bringing some vitamin A in this manner to the liver throughout fetal life, there is reason to suspect some difficulty in its withdrawal from the liver to the rest of the body by a reverse process after birth. Lewis⁴⁹ has found the concentration in the blood during the neonatal days to be rather below the level which a well-stocked liver might be expected to provide. The gradual rise in blood vitamin A level which has been observed to take place thereafter must be largely due to increased food ingestion, but failure of ingestion can hardly be the only reason for the low blood levels in the first week, when the liver appears able

to furnish vitamin A in quantity if it could be removed to the blood. In fact, even when an excess of dietary vitamin A is supplied (and absorbed) during the neonatal period the low blood levels are but little raised. This further suggests an avidity on the part of the liver, and a peculiar stability of the vitamin stored there.⁵²

It is less easy to state the requirement for vitamin A in the diet of the newborn infant than that for some of the other accessory food substances, and the present state of knowledge does not allow generalizations upon the broad effects of a marginal intake. Moreover, the publication of investigational results in varying types of units does not allow one study to be easily compared with another. However, something can be said about colostrum, human milk, and cow's milk as sources of vitamin A for the infant. Two investigations have shown that human colostrum contains a much greater amount than the milk which is afterwards secreted by the mother;^{54,55} this relationship applies to both vitamin A and carotenoid content. While the colostrum of lactating women contains almost twice as much total vitamin A activity as does the milk thereafter, it is interesting that the colostrum of the cow is as much as 10 to 100 times richer in vitamin A than is ordinary cow's milk. The difference is not that human *colostrum* is so much poorer in vitamin A than is cow colostrum, but that human *milk* is very much richer in the vitamin than is cow's milk. The average total biologic activities of vitamin A and carotenoids in human colostrum and milk have been determined by Dann to be 632 and 346 international units per 100 cc. respectively; for cow colostrum and milk the comparable figures are about 1000 and 35 international units respectively. In Dann's work⁵⁵ it was shown that the vitamin A and carotenoid content of human colostrum or milk could not be increased by the feeding of cod liver oil to a test group of mothers during their pregnancies. In the light of present knowledge, however, a nursing infant receives more than adequate vitamin A during newborn existence and thereafter, while an infant fed whole cow's milk probably has at least a satisfactory intake. Certainly a bottle-fed infant receiving a fish-liver supplement of vitamin D is being very well supplied with vitamin A by the same process.

More is known of **ascorbic acid** metabolism than of the physiology of any other accessory food substances during newborn life, since for several years a simple and reliable method of assay has been available. Exact knowledge is, however, wanting as to the relationship between plasma ascorbic acid levels and the state of ascorbic acid reserves in the body, and, what is more important, as to the total effects of deficiency upon fundamental physiologic processes. The discovery by Levine and others⁵⁶ that incomplete

metabolism of certain amino acids could be corrected by administering suitable amounts of ascorbic acid to premature infants has indicated how much more than the integrity of intercellular tissues may be at stake. Dann⁵⁷ has recently brought forth evidence that full-term infants may exhibit the same inadequacy of amino acid metabolism as do premature subjects when insufficient ascorbic acid is provided them. It is probable⁵⁸ that a group of more or less fundamental enzymatic reactions may require ascorbic acid for their normal function, or at least that this is the case in premature and probably in other newborn infants, if not during all ages of life.

In the absence of adequate data concerning the amount of ascorbic acid in the tissues of normal adults, it is difficult to evaluate information from analyses of such organs as the liver in fetuses and still-born infants. The fresh liver tissue of 56 such subjects examined by Toverud⁵⁹ contained from 2.7 to 10.4 mgm. ascorbic acid per 100 gm., with an average of 7.01 for full term infants and 6.05 for prematures. Her figures cover a range which bordered on the 3 mgm. of ascorbic acid per 100 gm. of liver which is said to characterize experimental scurvy in the guinea pig. They also show an apparent tendency for the vitamin C reserves to increase with length of gestation. Considerably higher concentrations were found by Ingalls,⁶⁰ the average in 8 stillborn infants in his study being 38.5 mgm./100 gm. liver, and the figure then declining to an average of 28.2 in seventeen infants dying in the first month, and to 10.8 in others surviving for one to four months. While it is probable that autopsy material from these later groups represents far less "normal" tissues than that from stillbirths, the results suggest a tendency for ascorbic acid depletion during the early weeks and months of life. There is some reason then to believe that if the maternal diet has been adequate, the newborn infant begins life with considerable reserves of ascorbic acid to be expended thereafter until its own nutrition can re-accumulate them.

In the cord blood at birth the level of vitamin C has repeatedly been demonstrated to reflect, but to be well above, that simultaneously present in the mother's blood.^{61,65} In Manahan and Eastman's⁶³ work the mean level of fetal ascorbic acid (at premature and full term delivery) was 1.15 mgm./100 cc. plasma, the maternal 0.38 mgm.; so that on the fetal side of the placenta a concentration of a crystalline substance was being maintained at almost three times its concentration on the other side. This, as the investigators point out, is a clear example of selective placental permeability, particularly striking since the human subject is supposedly unable to synthesize vitamin C. A decrease occurs immediately after birth. In one study the average umbilical blood level of 1.2 mgm./100 cc.

plasma had fallen to 0.7 mgm. at 72 hours.⁶⁵ After this the plasma levels appear to follow the dietary level of ascorbic acid, being higher if the infant is nursing from a well-nourished mother or taking a supplement, than if a cow's milk formula be the only source of vitamin C. Raw cow's milk under market conditions contains between 1 and 2 mgm./100 cc.⁶⁶ as compared with 3 to 4.5 mgm. in human milk.⁶⁷ A two week old infant receiving a usual formula (even if unboiled) would thus obtain only about 10 mgm. of ascorbic acid as compared to an intake of some 28 mgm. provided by an equally nourishing amount of human milk. The concentration of vitamin C in milk depends upon what the mother eats, and can be promptly raised by improving a sub-optimal maternal diet.^{68,70} It should here be mentioned that most agencies selling breast milk quite properly pasteurize their product, which must greatly diminish the ascorbic acid of purchased human milk.

Just how much vitamin C constitutes the best intake for the newborn infant cannot be stated, but it is claimed⁶⁹ that the optimum requirement may be even as high as 40 to 50 mgm. per day. In view of the error in metabolism which it corrects, of its probable other effects as yet unknown, and the report that a non-scorbutic neonatal disease entity is cured by its administration,⁷¹ it would seem that while the nursing infant may be securing adequate ascorbic acid, the premature and the bottle-fed infant should receive a daily supplement of 25 mgm. (and perhaps more) by the second or third week of life.

Knowledge of the "**vitamin B complex**" has not reached a sufficiently complete state for profitable presentation here. None of the numerous substances now known to compose the "complex" has been reported as at fault in any pathological states of newborn life, with the possible exception of rare instances of beriberi in extremely young infants whose nursing mothers were deficiently nourished, and of a premature infant with labial lesions which responded to riboflavin.⁷² No facts are available as to the transport of such factors as thiamin, riboflavin, and niacin from mother to fetus, nor as to the infant's reserves at birth. Cow's milk is usually considered a fair source of thiamin, but a few recent observations^{73,74} have raised questions as to the adequacy of human milk in this respect. Riboflavin is amply provided by cow's milk, though the amount of niacin is less, and may even be marginal. Until much more evidence becomes available it would be unwise to consider the unlikely possibilities of deficiency of any one of these factors in newborn infants receiving generally adequate diets.

The metabolism of vitamin K has been discussed in Chapter V.

CLINICAL SUMMARY

The reserves of the newborn infant with regard to minerals and vitamins are dependent upon the maternal diet and health, but the effects of this dependence, so far as the infant is concerned, are conditioned by the natural avidity of the fetus. Thus, the baby is not usually born with a significant mineral or vitamin deficit unless the maternal stocks available to it are extremely meager. A second point of general importance is that neonatal deficiencies in these substances ordinarily do not declare their presence by giving rise to symptoms until some time after birth, or indeed after the neonatal period. In this field the clinician's function is thus one of preventing the later development of deficiency states rather than treating their symptoms; he will seldom or never have an opportunity to see manifestations of mineral or vitamin lack in the days immediately following birth.

Biochemical measurements from blood samples will rarely be useful at the time when prevention of disturbance should be under consideration. Actually the blood **calcium** and inorganic **phosphorus** levels are generally within normal limits. Calcium and phosphorus values in samples from the umbilical vessels are usually slightly higher than in the maternal blood. The calcium tends to fall from about 11 to about 10 mgm. in the first few days after birth, while the phosphorus is rising from 5.5 to 6.0 mgm. The reason for this may be a "physiological" hypoparathyroidism; whatever the cause the effect may account for the occasional tetany of the newborn. The changes are transient and self-righting phenomena. Neonatal blood calcium measurements are not different in prematures from their levels in full-term infants.

While these minerals are held at reasonably stable and normal levels in the blood serum, extraordinary differences depending upon the amounts ingested may occur in the degree of their deposition in the body tissues. Retention of calcium and phosphorus is lowest with breast milk feeding and highest with an intake of cow's milk plus **vitamin D**. Although retention may be multiplied many times by such a dietary shift, there is no evidence that a superior type of bone results from this "super-mineralization." In fact, the type of bone built under human milk nutrition is less apt to be rachitic than that resulting from feeding with cow's milk plus insufficient vitamin D, even though several times as much calcium and phosphorus are being retained under the latter circumstances.

The pediatrician will do well to remember: 1, that premature and small babies are more apt and more prompt to develop rickets as they grow than are babies of greater birth weight; 2, that cow's

milk allows (and induces) the greatest assimilation and retention of bone-forming minerals; 3, that these are unlikely to be formed into healthy bone unless vitamin D is supplied; and 4, that such a supplement is needed well before any clinical signs of deficiency have appeared. He ought therefore to advise the daily administration of 400 to 800 I.U. of vitamin D by the second or third week of life whatever the source of minerals, and to increase this amount in premature infants. Under any ordinary circumstances the dietary addition of more minerals than those in milk is not indicated.

A decidedly marginal supply of **iron** is available for the first weeks of newborn life, and it is known that cow's milk is a still poorer source of this element than is human milk. Questions concerning neonatal iron requirements are confused when interpreted in terms of hemoglobin and erythrocytes, both of which undergo a quite normal decline under any regimen in early infancy. There is reason to doubt that this "physiological anemia" can be prevented by increasing dietary or medicinal iron (even granting the infant's powers of retaining it) early in the anemic period. Nothing seems to be gained by beginning the ingestion of extra iron very soon after birth, except the comfort that it will be available when in the course of his development the infant finds himself able to convert some of it into hemoglobin. In short, the more definite and "pathologic" an anemia has become in infancy, the more likely is ingested iron to be effective in relieving it, whereas the earlier such iron is provided the less will be the degree of its utility. So that beyond being ready to prescribe iron more or less therapeutically and for sufficient indications after the first month or two of life, the physician will do well merely to remember that nursing provides a somewhat less critical level of intake than bottle feeding, and to be observant for remediable anemia.

Although individual or even successive measurements of the **ascorbic acid (vitamin C)** in the blood do not offer highly reliable indications as to ascorbic acid nutrition, it appears that the blood level in the infant at birth reflects but is considerably above that of its mother. An immediate fall then occurs, from an ascorbic acid content of about 1.2 mgm./100 cc. plasma at birth to about 0.7 mgm. at 72 hours, after which the plasma level follows the dietary level of ascorbic acid, being higher if the infant is nursing from a well-nourished mother, or taking a supplement of the vitamin, than if a boiled milk formula be the only source of the vitamin provided. Raw cow's milk under market conditions contains between 1 and 2 mgm./100 cc. as compared with from 3 to 4.5 mgm. in human milk. By the end of the second week, an infant receiving a usual

amount of formula, even though unboiled, would obtain only about 10 mgm. of ascorbic acid, as against an intake of some 28 mgm. by a nursing infant. It would seem that while the nursing infant may be securing adequate ascorbic acid, the premature and the bottle-fed baby should receive a supplement of at least 25 mgm. (or $1\frac{1}{2}$ –2 oz. of orange juice) by the third week of life.

Neither clinical experience nor chemical measurements have yet indicated that infants during the neonatal period are likely to suffer from deficiencies of other vitamins such as **vitamin A**, **thiamin**, **riboflavin**, or **niacin**, at least so long as present day methods of feeding are practiced. A nursing infant certainly receives sufficient vitamin A, while an artificially fed one probably does so. The provision of a fish oil source of vitamin D obviates any possibility of vitamin A shortage. The members of the "vitamin B complex" may be assumed to be adequate in breast feeding or formulae until some evidence, particularly of clinical nature, can be found to indicate the opposite.

BIBLIOGRAPHY

1. SHOHL, A. T.: *Mineral Metabolism*, New York, Reinhold Publishing Corporation, 1939.
2. STEARNS, G.: Mineral metabolism of normal infants, *Physiol. Rev.* 19: 415, 1939.
3. GIVENS, M. H., and MACY, I. G.: Chemical composition of human fetus, *J. Biol. Chem.* 102: 7, 1933.
4. SWANSON, W. W., and IOB, V.: Growth of fetus and infant as related to mineral intake during pregnancy, *Am. J. Obst. & Gynec.* 38: 382, 1939.
5. BOOHER, L. E., and HAUSMANN: Calcification of the tibia of the normal new-born infant, *J. Biol. Chem.* 94: 194, 1931.
6. FINOLA, G. C., TRUMP, R. A., and GRIMSON, M.: Bone changes in fetus following administration of dicalcium-phosphate and viosterol to pregnant mother, *Am. J. Obst. & Gynec.* 34: 955, 1937.
7. (a) MICHEL, C.: Recherches sur la nutrition normale du nouveau-né. Échanges nutritifs Azotes et Salins, *L'Obstetrique* 1: 140, 1896.
- (b) MICHEL, C.: Sur le lait de femme et l'utilisation de ses matériaux nutritifs, *L'Obstetrique* 2: 518, 1897.
8. LANGSTEIN, L., and NIEMANN, A.: Ein Beitrag zur Kenntniss der Stoffwechselvorgänge in den ersten vierzehn Lebenstagen normaler und frühgeborener Säuglinge, *Jahrb. f. Kinderh.* 71: 604, 1910.
9. (a) BIRK, W.: Beiträge zur Physiologie des Neugeborenen Kindes; die Bedeutung des Kolostrums, *Monatschr. f. Kinderh.* 9: 595, 1910.
- (b) BIRK, W.: Untersuchungen über Stoffwechsel des Neugeborenen Kindes, Leipzig, Barth, 1912.
10. SWANSON, W. W.: Composition of growth; full-term infant, *Am. J. Dis. Child.* 43: 10, 1932.
11. ROMINGER, E., FASOLD, H., and MEYER, H.: *Methodik zur Durch-*

- führung langfristiger ununterbrochener Mineral- und Stickstoffwechsel-untersuchungen beim Säugling, *Arch. f. Kinderh.* 88: 179, 1929.
12. SHOHL, A. T., WAKEMAN, A. M., and SHORR, E. Y.: Mineral metabolism on a high mineral diet, *Am. J. Dis. Child.* 35: 576, 1928.
 13. BENJAMIN, H. R., GORDON, H. H., and MARPLES, E.: Calcium and phosphorus requirements of premature infants, *Am. J. Dis. Child.* 65: 412, 1943.
 14. PAFFRATH, H., and MASSART, J.: Langfristige Untersuchungen des Mineral- und Wasserstoffwechsels bei Frühgeborenen, *Ztschr. f. Kinderh.* 54: 343, 1933.
 15. TODD, W. R., CHUNARD, E. G., and WOOD, M. T.: Blood calcium and phosphorus in the newborn, *Am. J. Dis. Child.* 57: 1278, 1939.
 16. DENZER, B. S., REINER, M., and WIENER, S. B.: Serum calcium in newborn, *Am. J. Dis. Child.* 57: 809, 1939.
 17. PALACIOS COSTA, N., ESCARDO, F., and SCHERE, S.: Calcemia en el recién nacido, *Rev. Soc. argent. de biol.* 10: 273, 1934.
 18. HESS, A. F., and MATZNER, M. J.: Rickets in relation to the inorganic phosphate and calcium in maternal and fetal blood, *Am. J. Dis. Child.* 26: 285, 1923.
 19. BOGERT, L. J., and PLASS, E. D.: The calcium and magnesium content of fetal and maternal blood serum, *J. Biol. Chem.* 56: 297, 1923.
 20. KRANE, W.: Kalium und Kalzium im mütterlichen und kindlichen Serum sowie im Gesamtblut von Mutter und Kind, *Ztschr. f. Geburts. u. Gynäk.* 97: 22, 1930.
 21. BAKWIN, H., and BAKWIN, R. M.: Factors influencing calcium concentration in serum of new-borns. *Am. J. Hyg.* 15: 766, 1932.
 22. RAY, H. H., and PHATAK, N. M.: Diffusible blood serum calcium in normal new-born infants, *Am. J. Dis. Child.* 40: 549, 1930.
 23. ANDERSCH, M., and OBERST, F. W.: Filterable serum calcium in late pregnant and parturient women, and in newborn, *J. Clin. Investigation* 15: 131, 1936.
 24. BOKELMANN, O., and BOCK, A.: Über die Zustandsform des Calciums im Serum während der Gestationszeit, *Arch. f. Gynäk.* 133: 739, 1928.
 25. McLEAN, F. C., and HASTINGS, A. B.: The state of calcium in the fluids of the body. I. The conditions affecting the ionization of calcium, *J. Biol. Chem.* 108: 285, 1935.
 26. McKELLIPS, G. M., DeYOUNG, I. M., and BLOOR, W. R.: The distribution of phosphoric acid in the blood of normal infants, *J. Biol. Chem.* 47: 53, 1921.
 27. STEARNS, G., and WARWEG, E.: Studies of phosphorus of blood; partition of phosphorus in whole blood and serum, serum calcium, and plasma phosphatase from birth to maturity, *J. Biol. Chem.* 102: 749, 1933.
 28. SONTAG, L. W., MUNSON, P., and HUFF, E.: Effects on fetus of hypervitaminosis D and calcium and phosphorus deficiency during pregnancy, *Am. J. Dis. Child.* 51: 302, 1936.
 29. BULLOCK, J. K.: The physiologic variations in the inorganic blood phosphorus content at the different age periods, *Am. J. Dis. Child.* 40: 725, 1930.
 30. BAKWIN, H.: Tetany in newborn infants; relation to physiologic hypoparathyroidism, *J. Pediat.* 14: 1, 1939.

31. ELIOT, M. M., and PARK, E. A.: Rickets, in Vol. 1, Practice of Pediatrics, Edited by Joseph Brennemann, Hagerstown, W. F. Prior Company, 1942.
32. BARNES, D. J., and MUNKS, B.: Serum phosphatase, calcium and phosphorus values in infancy, Proc. Soc. Exper. Biol. & Med. 44: 327, 1940.
33. KAY, H. D.: Phosphatase in growth and disease of bone, Physiol. Rev. 12: 384, 1932.
34. POMMERENKE, W. T., HAHN, P. F., BALE, W. F., and BALFOUR, W. M.: Transmission of radio-active iron to human fetus, Am. J. Physiol. 137: 164, 1942.
35. TOVERUD, K. U.: Investigation on iron store of newborn infants, Acta paediat. (Supp. 1) 17: 136, 1935.
36. IOB, V., and SWANSON, W. W.: A study of fetal iron, J. Biol. Chem. 124: 263, 1938.
37. STEARNS, G., and MCKINLEY, J. B.: Conservation of blood iron during period of physiological hemoglobin destruction in early infancy, J. Nutrition 13: 143, 1937.
38. JOSEPHS, H. W.: Anaemia of infancy and early childhood, Medicine 15: 307, 1936.
39. JOSEPHS, H. W.: Iron metabolism in infancy; factors influencing iron retention on ordinary diets, Bull. Johns Hopkins Hosp. 65: 145, 1939.
40. STEARNS, G., and STINGER, D.: Iron retention in infancy, J. Nutrition 13: 127, 1937.
41. TOVERUD, K. U., and ENDER, F.: Vitamin A and D content of liver of newborn infants, Acta paediat. 18: 174, 1935.
42. NICHOLAS, H. O., and KUHN, E. M.: The role of calcium, phosphorus and vitamin D in pregnancy, J. Clin. Investigation 11: 1313, 1932.
43. SWANSON, W. W., and IOB, L. V.: Calcium and phosphorus content of offspring after feeding vitamin D to mother rat, Am. J. Dis. Child. 49: 43, 1935.
44. DUNHAM, E. C.: Rickets in an infant of thirty-four days, Am. J. Dis. Child. 26: 155, 1923.
45. HARRIS, R. S., and BUNKER, J. W. M.: Vitamin D potency of human breast milk, Am. J. Pub. Health 29: 744, 1939.
46. DRUMMOND, J. C., GRAY, C. H., and RICHARDSON, N. E. J.: Antirachitic value of human milk, Brit. M. J. 2: 757, 1939.
47. WENDT, H.: Über den Carotin-Vitamin A-Stoffwechsel des menschlichen Fetus. Carotin- und Vitamin A-Bestimmungen im Schwangerenblut, in Placenten, im Nabelschnurblut und in fetalen Lebern, Klin. Wchnschr. 15: 222, 1936.
48. WOLFF, L. K.: On quantity of vitamin A present in human liver, Lancet 2: 617, 1932.
49. LEWIS, J. M., BODANSKY, O., and HAIG, C.: Level of vitamin A in blood as index of vitamin A deficiency in infants and in children, Am. J. Dis. Child. 62: 1129, 1941.
50. GAETGENS, G.: Der Übergang von Carotin und Vitamin A aus dem mütterlichen in den kindlichen Blutkreislauf, Arch. f. Gynäk. 164: 398, 1937.
51. CLAUSEN, S. W., and McCOORD, A. B.: Carotinoids and vitamin A of blood, J. Pediat. 13: 635, 1938.
52. LEWIS, J. M., BODANSKY, O., and SHAPIRO, L. M.: Regulation of level of vitamin A in blood of newborn infants, Am. J. Dis. Child. 66: 503, 1943.
53. BYRN, J. N., and EASTMAN, N. J.: Vitamin A levels in maternal and

- fetal blood plasma, *Bull. Johns Hopkins Hosp.* 73: 132, 1943.
54. VAN EEKELEN, M., and DE HAAS, J. H.: Carotene and vitamin A in human milk, especially in colostrum, *Geneesk. Tijdschr. v. Nederl.-Indië*, 74: 1201, 1934.
 55. DANN, W. G.: Transmission of vitamin A from parents to young in mammals; vitamin A and carotenoid contents of human colostrum and milk, *Biochem. J.* 30: 1644, 1936.
 56. LEVINE, S. Z., GORDON, H. H., and MARPLES, E.: Defect in the metabolism of tyrosine and phenylalanine in premature infants: II. Spontaneous occurrence and eradication by vitamin C, *J. Clin. Investigation* 20: 209, 1941.
 57. DANN, M.: The influence of diet on the ascorbic acid requirement of premature infants, *J. Clin. Investigation* 21: 139, 1942.
 58. KING, C. G.: Vitamin C, ascorbic acid, *Physiol. Rev.* 16: 238, 1936.
 59. TOVERUD, K. U.: Vitamin C content of liver of newborn infants, *Arch. Dis. Childhood* 10: 313, 1935.
 60. INGALLS, T. H.: Ascorbic acid requirements in early infancy, *New England J. Med.* 218: 872, 1938.
 61. WAHREN, H., and RUNDQVIST, O.: Über den Ascorbinsäuregehalt des Blutes von Mutter und Frucht, *Klin. Wehnschr.* 16: 1498, 1937.
 62. BROESTRUP, P. W.: Studies of latent scurvy in infants; content of ascorbic acid in blood-serum of women in labour and in children at birth, *Acta paediat.* 19: 328, 1937.
 63. MANAHAN, C. P., and EASTMAN, N. J.: Cevitamic acid content of fetal blood, *Bull. Johns Hopkins Hosp.* 62: 478, 1938.
 64. SNELLING, C. E., and JACKSON, S. H.: Blood studies of vitamin C during pregnancy, birth and early infancy, *J. Pediat.* 14: 447, 1939.
 65. MINDLIN, R. L.: Variations in concentration of ascorbic acid in plasma of newborn infant, *J. Pediat.* 16: 275, 1940.
 66. HAWLEY, E. E.: Vitamin C content of milks: raw, pasteurized, and baby formulas, *J. Am. Dietet. A.* 14: 275, 1938.
 67. INGALLS, T. H., DRAPER, R., and TEEL, H. M.: Vitamin C in human pregnancy and lactation; studies during lactation, *Am. J. Dis. Child.* 56: 1011, 1938.
 68. KASAHARA, M., and KAWASHIMA, K.: Beitrag zur Kenntnis des Vitamin C—Gehaltes in der Colostralmilch, *Klin. Wehnschr.* 15: 1278, 1936.
 69. SELLEG, I., and KING, C. G.: Vitamin C content of human milk and its variation with diet, *J. Nutrition* 11: 599, 1936.
 70. WIDENBAUER, F., and KÜHNER, A.: Ascorbinsäurestudien an stillenden Frauen, *Ztschr. f. Vitaminforsch.* 6: 50, 1937.
 71. LEY, L.: Die Bedeutung des Vitamin C für das Neugeborene, *Klin. Wehnschr.* 16: 1425, 1937.
 72. STEVENSON, S. S.: Possible ariboflavinosis in a premature infant, *Yale J. Biol. & Med.* 14: 403, 1942.
 73. KENDALL, N.: Thiamin content of various milks, *J. Pediat.* 20: 65, 1942.
 74. KNOTT, E. M., KLEIGER, S. C., and SCHULTZ, F. W.: Is breast milk adequate in meeting thiamine requirements of infants? *J. Pediat.* 22: 43, 1943.

Chapter XI

RENAL PHYSIOLOGY: REGULATION OF ELECTROLYTES AND WATER

- Section 1* . . . Renal Function in Neonatal Life
Section 2 . . . Control of Electrolytes and Water
Section 3 . . . Clinical Summary
-

RENAL FUNCTION IN NEONATAL LIFE

THE KIDNEYS HAVE no essential responsibility during fetal life, because the excretory requirements of the fetus can be completely satisfied by the placenta. This is demonstrated by the occasional birth of otherwise fully developed infants lacking kidneys, or without patent urinary passages.¹ Nevertheless, the bladder of the fetus contains urine by the fourth month of gestation, and urea appears in the amniotic fluid even earlier than this. What portion of the amniotic fluid is contributed by the fetal kidneys is not known; there is evidence that the amount is not inconsiderable and is responsible for the hypotonicity of this fluid,² but of course the renal component must be added very gradually.^{1,3} Thus, the fetal kidneys appear to produce urine slowly, the urine itself is known to be distinctly dilute and hypotonic as compared with blood plasma, and the whole process is of no significance to the organism unless one may speak of it as a kind of practice for essential activity to come. Although the bladder at birth contains up to about 45 cc. of urine⁴ the figure means little because of the readiness and the variability of overflow into the amniotic sac.

The kidneys themselves yield certain morphologic evidence as to their preparedness for functional activity during and after gestation. It is well known that the gross lobulation which characterizes their fetal structure remains more or less discernible throughout the first year after birth. Potter⁵ has investigated the rate at which the development of glomeruli reaches full morphological maturity, with results of significance as indications of the maturity of the total organism. A so-called "nephrogenic zone," in which glomerular units were still being developed, was shown to be present in almost all subjects weighing 2000 gm. (4.4 lb.) or less, and to have disappeared in almost all weighing 2500 gm. (5.5 lb.) or more. In

terms of gestational age this dividing point between renal immaturity and maturity was reached at about the 35th week, so that by this criterion full development appears to be established about a month before birth normally occurs. That the degree of use to which the cells are put makes no apparent difference to this developmental schedule is clearly brought out by the observation

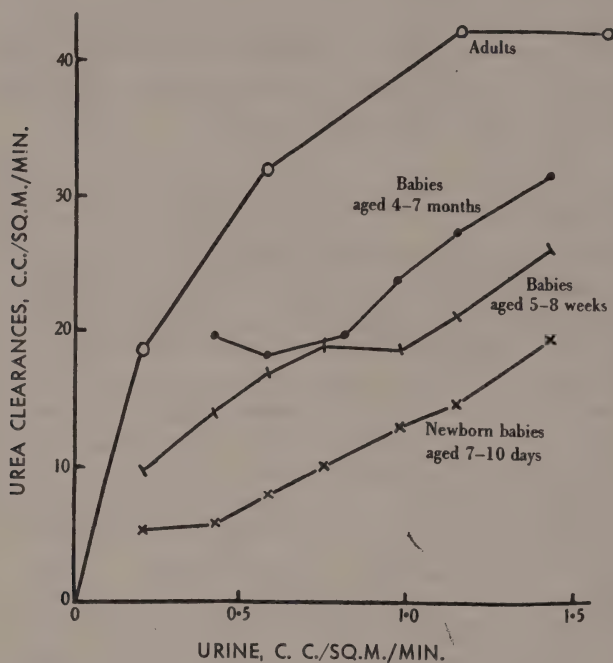


FIGURE 31

A comparison of the average urea clearances of adults and of infants at three different ages, on the basis of body surface. (McCance, Young, *J. Physiol.*, 99: 265, 1941.)

that its rate of progress shows no alteration depending upon the event of birth; a particular degree of glomerular development is attained at a standard time after conception whether the organism is living in the uterus as a fetus or outside it as a prematurely born infant. The kidneys differ in this regard from such other organs as the lungs, the heart, and the adrenal, which reflect the fact of birth by profound alterations in morphology. A sudden rupture or bursting of the epithelial layer covering the glomerular tufts has been said to occur at birth⁶ and thus to bring about an immediate increase in the ease of glomerular filtration, but it is unlikely that

any abrupt phenomenon of this sort actually occurs, and much more probable that all renal developments are gradual ones.

Before discussing the different substances in whose regulation it plays a major role, something may be said of the general excretory adequacy of the neonatal kidney as revealed by tests of its function. The recent investigations of McCance and Young;⁷ Young, Hallum and McCance;⁸ and Gordon, Harrison and McNamara⁹

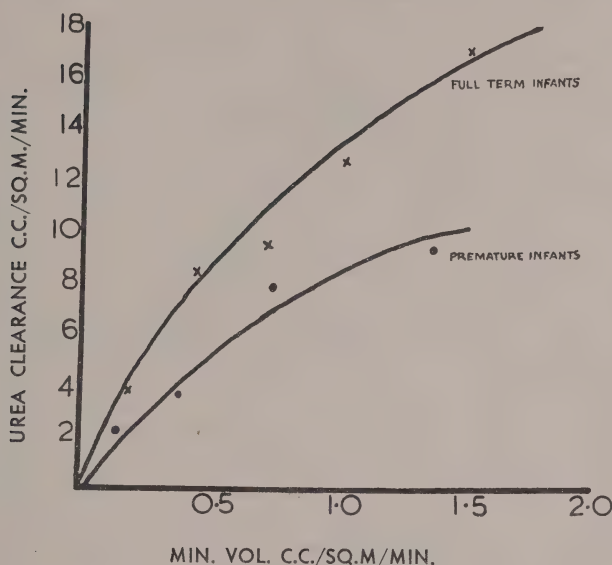


FIGURE 32

Average urea clearances of full-term and premature infants. (Young, Hallum, McCance, *Arch. Dis. Child.*, 16: 243, 1941.)

are in substantial agreement that the clearance of urea from the blood is less efficient in newborn subjects than in adults, and that this deficiency is still greater in premature than in full-term infants. This appears to be demonstrable upon any basis of comparison, including not only the standard one of clearance per unit of body surface area, but also the perhaps more significant one of clearance per unit of kidney weight.⁷ The degree of this deficiency is shown in the three accompanying charts, reproduced through the kindness of Dr. McCance. The acquisition of a renal function comparable in flexibility and alertness with that of the adult appears to be a very gradual process, and, like the morphological development which precedes it, undergoes no sudden transition either in the newborn period or later. Nevertheless, a chart here reproduced from

Gordon's work (Figure 34) shows that within a few weeks' time the urea clearances of individual infants usually show a definite improvement.

An unsettled relationship exists between urea clearance and variations in rate of urine formation by the kidneys of the newborn. It will be noted from the charts reproduced from the work of McCance and his colleagues that the urea clearance of their subjects (aged from 3 to 18 days) was directly related to the minute

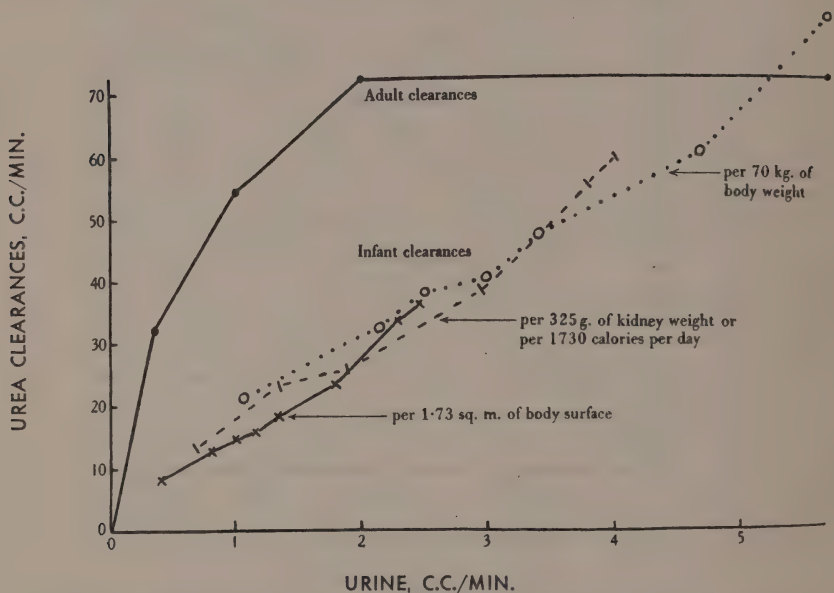


FIGURE 33

Relationship between neonatal and adult urea clearances, showing that, whatever the basis of comparison, the performance of the infant is inferior to that of the adult. (McCance, Young, *J. Physiol.*, 99: 265, 1941.)

volume of urine formed. Actually the minute volumes of these infants were not abnormal when compared with the volume of urine produced by adults if both were reduced to standard surface area. Nevertheless, McCance and Young have clearly demonstrated from their data, presented here in Figure 33, that a newborn infant could not be expected to equal the urea clearance of an adult unless the rate of urine formation by the former were increased to an amount which would correspond to about 5.3 cc. per minute in the latter. As this would represent a diuresis of about five times the ordinary adult urine volume, a striking dependence of the somewhat inadequate urea clearance upon urinary output would appear

to limit the renal function of newborn infants, whether premature or full-term. On the other hand, when Gordon and his colleagues put the matter to the test by increasing the urine output in individual subjects by from 25 to 100 per cent, they found that the clearances of these infants actually remained quite constant. The

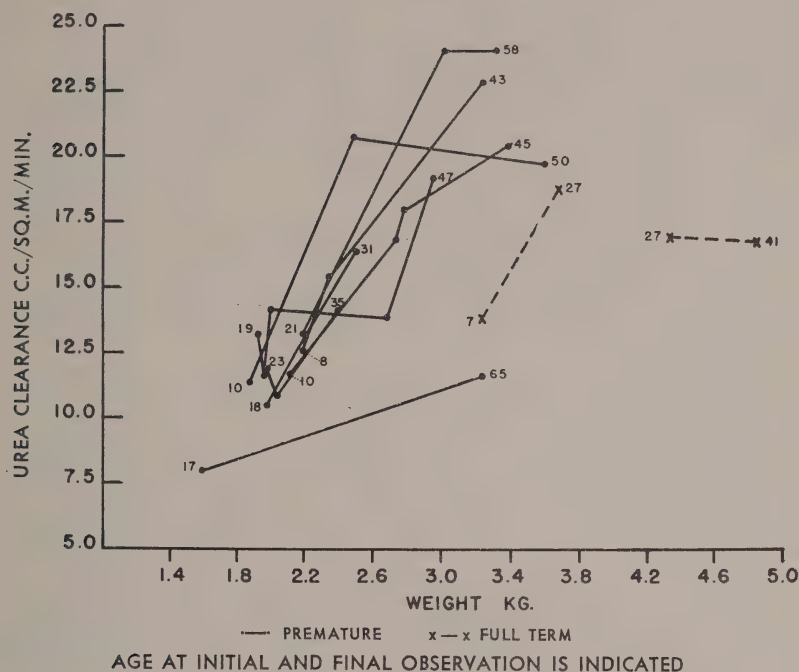


FIGURE 34

Improvement in urea clearance with increasing age of neonatal subjects. (Gordon, Harrison, McNamara, *J. Clin. Investigation*, 21: 499, 1942.)

infants thus studied by them were slightly older (8 to 73 days) than those studied by McCance and Young, and there may have been explanations for the disagreement of results because of different experimental methods. In any event, the general principle holds that by a delicate functional test the kidneys of newborn infants do not appear to perform their work as capably as those of adults, nor is this deficiency overcome until some time after morphological evidence of anatomical maturity is observable. In passing, the apparent relationship of urine formation to body surface obviously requires the infant to produce a relatively large volume of urine and thus may allow him a better clearance than would be the case

if body mass controlled urine formation. On the other hand, the large surface area of the infant also demands an uneconomical expenditure of water by extra-renal channels as insensible loss.

Since urea is filtered from the blood in the glomeruli and then partially reabsorbed by the tubular epithelium, these tests do not tell us whether the neonatal kidney is at fault with particular regard to glomerular filtration or to tubular reabsorption. Inulin clearance, which is a measure of glomerular filtration only, has given further information in newborn subjects suggesting that deficiency of glomerular filtration probably outweighs deficiency of tubular activity. McCance and Young found the inulin clearances of a small group of neonatal subjects to have somewhat less than half the values expected for adults and to vary with the minute volumes, whereas the ratio of urea clearance to inulin clearance remained fairly constant in spite of minute volume variations. This evidence indicates a parallelism between glomerular filtration and urea clearance as though shortcomings of the former might explain those of the latter.

The English investigators have given particular attention to the osmotic pressure of the urines voided by their newborn subjects. This they have shown to be consistently low, indeed so much so that the urines were regularly hypotonic when compared to blood plasma. These results would seem to be related to low clearances not only of urea but also of sodium and chloride from the plasma, and this appears to be the case especially in premature infants.⁸ The clinical importance of these observations is considerable, particularly in view of the frequency with which edema is encountered in premature and full-term infants. Edema may occur either spontaneously as is often the case in premature babies, or as an unanticipated result of the injudicious administration of salt solutions to any newborn patient. A renal mechanism incapable of removing solids at greater concentrations than they are carried in the plasma (and thus in the general interstitial fluids) must obviously be unable to remove electrolytes from the body to such a degree that a prompt withdrawal of any excessive quantity of water would follow. Other observations have shown, however, that the excretion of a hypertonic urine can be forced to occur even in a premature infant, if the intake of salt is sufficiently increased.¹⁰ Indeed, urinary removal of electrolytes at a higher concentration than they normally maintain in blood plasma occurs in most neonatal subjects when spontaneously or artificially acquired states of edema begin to abate. Nevertheless, enough deficiency in the flexibility of renal function characterizes the neonatal period so that in clin-

ical dealings with very young infants electrolytes should be used with some caution.

The post-natal reduction of about 6 to 10 per cent of total body weight, usually referred to as the "physiological weight loss," is mainly the result of a net loss of body water.^{11,12} The first three or four post-natal days are attended by a diminution in the water content of the blood as demonstrated by refractometric and other studies.^{11,13,14} These show maximal deviations at the third or fourth day, after which the findings indicate an increase in blood hydration coincidental with the gain in weight which succeeds the physiological loss. Although a slight tendency to an increased water content of the blood continues thereafter for about six months,^{15,16} the post-natal interval actually represents a comparatively transient fluctuation of an otherwise steady and prolonged process of dehydration which begins in embryonic existence, continues through fetal development, and goes on as a gradual desiccation during extra-uterine life.¹⁷ Thus the water content of the total embryo at six weeks is about 97 per cent, that of the fetus at birth about 70 per cent, and that of the fully developed adult from 58 to 65 per cent.^{15,18-20} Viewed in this broader context, the sudden loss of water during the first few post-natal days and the recovery to (or beyond) normal hydration during the months thereafter may seem somewhat less significant. Still, the post-natal period witnesses a more abrupt dislocation of water economy than any other naturally occurring change of a similar sort. This must be taken into account in any discussion relating to renal activity in neonatal life.

The dehydration largely responsible for the physiological weight loss is due to water loss of an "insensible" nature, or, more explicitly, to the negative balance between intake by mouth and outgo from the lungs and skin. The urinary excretion of water is therefore scanty during the immediate post-natal period, as shown by the following figures representing averages of several different studies collected by Gundobin²¹ and amplified by Feldman:²⁰

AVERAGE URINARY OUTPUT

Day of Life	1st	2nd	3rd	4th	5th	6th
Urine—cc/24 hrs.	15.6	39.7	58	105.4	148	195.5

Although such small quantities of urine are voided, the specific gravity is said to be no higher than about 1.012 on the first day, with a decrease to between 1.003 and 1.004 on the sixth.²⁰ These figures bear out the supposition that the kidney in neonatal life finds difficulty in forming a concentrated urine, although it cannot

be insisted that excess amounts of all solid substances are normally presenting themselves for excretion during all of this time.

The clinician may be more interested in the appearance of albumin in the urine, since the tests and measurements mentioned above are not likely to be applied to many of his newborn patients. Tests for albumin have been so consistently positive, especially during the second to the fifth days after birth²²⁻²⁵ that it is to be considered a more or less "physiologic" constituent of the newborn infant's urine. Pfaundler²⁵ concludes that the positive reaction may often be due to mucin and not to albumin as such, but this has not been ascertained to be regularly the case. Albumin appears to be present even more frequently in the urine of premature than full-term subjects; Ewald²⁴ found that 75 per cent of the urines passed by infants weighing less than 3.5 kilograms reacted positively to tests for albumin while 69 per cent of specimens from infants weighing more than that amount at birth were positive. These two groups were aged from birth to ten days. At the latter age only 38 and 30 per cent of the two groups were albuminuric, so that positive tests in the third week are much more significant of pathology than those obtained earlier. Salmi²⁶ has shown somewhat more albuminuria to occur in normal infants born of albuminuric mothers, but this needs confirmation from a larger series of patients. Thus, although the kidney is a more or less completely developed organ at full-term birth, its functional efficiency appears to fall considerably below that attained later in life. Measurements of its output, and examinations of the state of the plasma, indicate a limitation in the amount of water available for renal purposes, which would increase the general excretory difficulties of the immediate post-natal period. Moreover, the albuminuria and the excessive uric acid excretion occurring coincidentally also testify to a certain amount of temporary strain upon the excretory mechanism in the the first few days after birth. Analyses of electrolyte, protein, and hydrogen ion concentration in the blood should indicate how successfully the kidneys cope with their essential responsibilities under these various disadvantages.

CONTROL OF ELECTROLYTES AND WATER

Few studies from large numbers of subjects are available as sources for accurate standards of the normal plasma electrolytes in the newborn infant. Perhaps the most useful measurements have been those obtained by Bruch and McCune, during their investigations of adrenal physiology,²⁷ and those appearing in a series of papers begun by Hoag and Kiser and continued by Marples and

Lippard.²⁸⁻³¹ Although this is not an extensive literature, the general agreement among its various results makes it a reliable one. In the following discussion of the important cations and anions of the blood, the data reported by these and other authors have been converted to milli-equivalents per liter (meq./L.) when they were otherwise expressed in the original.

A chart (Figure 35) from the work of Bruch and McCune²⁷ shows the remarkable steadiness with which **sodium** concentration

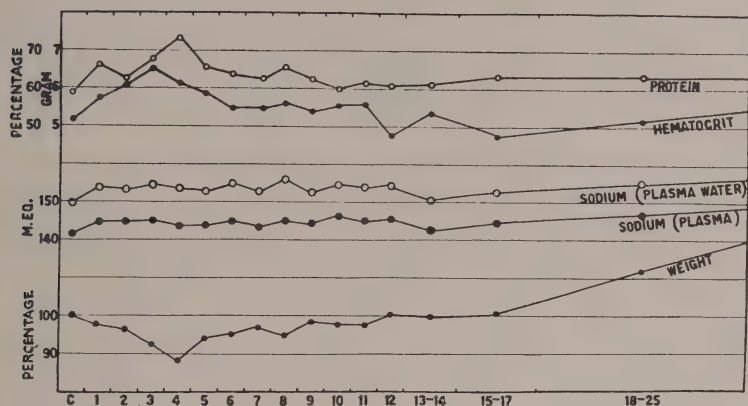


FIGURE 35

Variations in plasma sodium concentration and in other measurements during the first 25 days of life. C represents umbilical cord blood. (Bruch, McCune, *Am. J. Dis. Child.*, 52: 863, 1936.)

is maintained in the plasma from day to day during the neonatal period, despite the evidence of dehydration appearing in the accompanying curves for plasma protein, hematocrit, and weight. Although the chart portrays average amounts, the standard deviations for each were small, being seldom more than 5 meq./liter. The serum sodium values in umbilical cord blood at birth are very slightly higher than those of the mothers' blood samples taken at the same time, the relationship being 142 meq./L. as compared to 140.³² The change between this cord blood value and the slightly increased one of 143.5 to 146.5 meq./L, which is maintained for the next three to four weeks, takes place so quickly after birth that the sodium concentration of cord blood may represent only a temporary deviation from what may have been a higher figure just before labor. The constancy with which sodium concentration is maintained within reasonably narrow bounds through the days of readjustment after birth is not quite so well attested in every set of

analyses,⁷ but measurements of total base have shown only minor departures from a figure of about 152 meq./L.²⁹ Moreover, it has been learned that only slight variations from this figure for total base are produced by the experimental administration of alkali by mouth to infants of 3 to 10 days of age so that the newborn child appears to possess considerable powers for maintaining base ions at a fairly stable level.³¹ For some undiscovered reason, **potassium** has regularly been found to be elevated both at birth³³ and in the neonatal period.^{7,34} The difference between average figures of about 5.6 meq./L. in normal adults and 7.8 in newborn infants in McCance and Young's⁷ measurements of potassium is significant so far as potassium itself is concerned, but is of slight importance as a contribution to total base. **Calcium** has been considered in a previous chapter.

Most of the evidence with regard to **chloride ion** points to an increase in its concentration during the neonatal period, although at the time of birth the cord blood chlorides tend to be slightly below the maternal.^{22,32} McCance and Young⁷ found chloride ion to average slightly above 107 meq./L in the serum of infants aged 7 to 14 days, as against the normal of 104 for adults. This elevation, which may sometimes be of greater degree,²⁹ is probably explainable as a result of dehydration of the blood. Thus chloride ion appears to be most concentrated at the time of greatest weight loss, and tends to remain at higher levels as the weight falls in those infants showing "dehydration fever."³⁵ In prematures the chloride ion concentration is perhaps more variable than in full-term infants, and tends to be slightly lower, especially during the first 3 to 5 days, when an average figure of 104.5 meq./L has been obtained.⁸ In a small number of edematous prematures of like age the average chloride concentration was practically the same as in those without edema. In non-edematous premature infants somewhat higher chloride ion values (average 108.5 meq./L) occurred during the second and third weeks of life.⁸

The concentration of **bicarbonate ion** in the plasma of normal newborn infants is shown diagrammatically and numerically in Figure 36, as being 22.1 meq./L. This figure, derived by Branning³⁶ from Marples and Lippard's³⁰ data, is less than the one of 27 stated by Gamble³⁷ to represent the normal standard value. This deficiency in the bicarbonate fraction may be seen in the diagram to result from a slight deficiency of total base, an extension of the chloride, phosphate, and sulfate components, together with a deficiency reported in the organic acids. However, the large extension of the organic acid fraction in the plasma of well *premature* infants

and the further increase of this component in the plasma of acidotic prematures shown in Figure 36 has indicated³⁶ that the stated figure of 3.0 meq./L for these acid ions in the full-term newborn infant may be lower than is actually the case. Another series of measurements from full-term infants would be of interest.

Of perhaps more significance than the isolated fact of an average

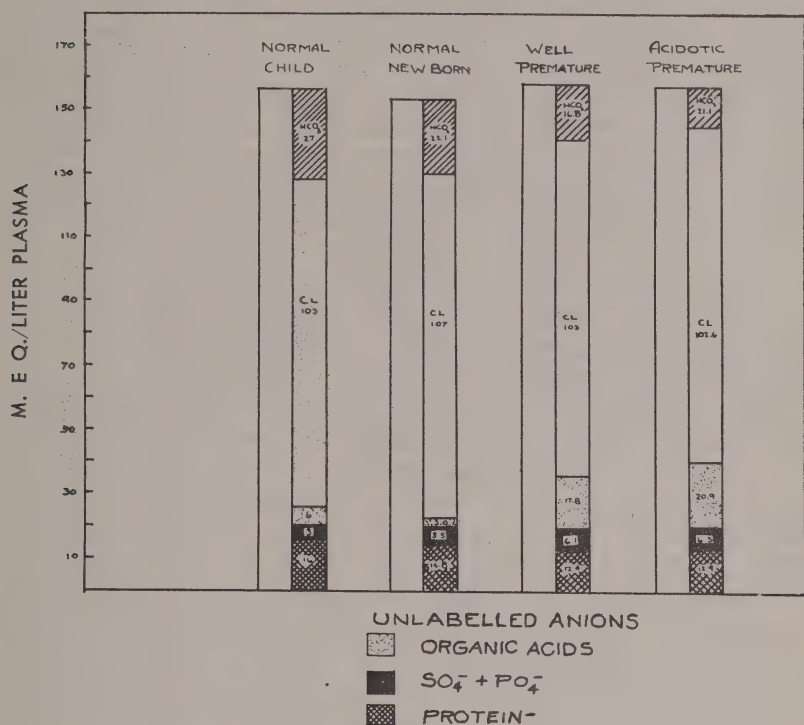


FIGURE 36

Distribution of plasma electrolytes in newborn infants as compared to the normal child.³⁷ The diagram was expanded and re-drawn from Branning's chart, in which the data for normal newborn infants were taken from Marples and Lippard.³⁰ (Branning, *J. Clin. Investigation*, 21: 101, 1942.)

bicarbonate value of 22.1 (corresponding to a CO_2 content of 49 vols. %) is the relative instability, during neonatal life, of those mechanisms which control acid-base equilibrium and more particularly the acid ion participants in this relationship. Studies^{30,31} have shown that disturbances in this equilibrium, as reflected by changes in plasma bicarbonate or carbon dioxide content, are produced in newly-born subjects by relatively minor changes in the diet. Thus

a shift from breast milk to the more acid cow's milk was shown to be followed by a decrease in plasma bicarbonate, whereas the daily addition of one gram or even less of sodium bicarbonate to the diet led to an increase in bicarbonate ion. Dietary alterations of a comparable degree were not sufficient to alter the acid-base composition of the blood in slightly older infants. The sensitivity to acid increase may be an expression of relatively inefficient renal function.³⁰ The increase in alkali reserve of newborn subjects given small increases in dietary base appears to result from a measurable decrease in the acid substances of the blood rather than from demonstrable increase in concentration of base.³¹ But since experimental alkali feeding of the newborn was accompanied by weight gain and by decrease in serum protein concentrations, Lippard and Marples³¹ argue that there may be an actual increase in the amount of total base retained, together with a sufficient retention of water so that base concentration per liter of serum is not increased.

The vagaries of serum protein levels during the general period of neonatal life, and the fact of their moderate deficiency, cannot be explained beyond the discussion presented in Chapter IX. Changes in protein concentration do not adequately explain occasionally observed states of edema, though they may be contributing factors.

The belief in a tendency toward a considerable acidosis as a fairly constant feature of neonatal life was largely the outgrowth of Yllpö's^{38,39} observations, based upon a chemical approach perhaps less valid than the direct measurement of hydrogen ion concentration. More recent determinations made upon (venous) serum have shown a pH which is rather narrowly regulated at an average value of 7.4 during the first week of life.²⁹ This indicates that whatever tendency to acidosis may be present is compensated, although the hydrogen ion concentration does shift to a larger or smaller figure for pH than its normal 7.4 if very slight changes are made toward either alkalinity or acidity of the food intake. The newborn infant's blood thus shows the presence of a very mild "metabolic" acidosis, arising from a minor deficiency in total base and a moderate increase in mineral acids, the combined effect being to diminish bicarbonate ion. The position of renal control in relation to the somewhat precarious equilibrium thus established cannot be exactly assessed. That the kidneys help to provide a fairly accurate adjustment under the usual circumstances of newborn life is apparent; that they are to be blamed in some degree for demonstrable deviations from entirely satisfactory adjustment under conditions of strain is probable. Whether the respiratory compensation to

this metabolic acidosis is as alert and efficient as in later life is also to be questioned. One sees occasional newborn infants with diarrhea sufficient to bring about a marked displacement of bicarbonate by stronger acid ions; in these patients it is not uncommon for expected hyperpnea to be absent.

Studies of the regulation of acid-base equilibrium in premature infants have given hints of organic acid accumulation to a degree hitherto unsuspected. These phenomena seem to occur both normally and, to a larger degree, as a result of certain pathological states. This field should be further explored in full-term newborn infants suffering from diarrheal disease, for clinical experience has shown that under such circumstances these babies show evidence of profound and incompletely explained disturbance. As is shown in Figure 36, adopted from Branning's³⁶ work, the plasma of apparently normal premature infants aged from 3 days to 2 months contains an important amount of organic acids; moreover, the excretion of these substances in the urine of such infants is two to five times as great as would be expected in the normal adult on the basis of the same body weight. Branning³⁶ found that the organic acids of either the blood or the urine were not the ordinary ketones, which have been rather conspicuously absent in all investigations,^{36,40} and lactic acid accounted for not more than 20 per cent of the organic acids excreted by apparently normal prematures.

Räihä's⁴⁰ recent work has shown that the organic acids excreted by full-term infants are also excessive in amount, and that at 24 hours of age the predominant one of these is pyruvic (pyroracemic) acid. Thereafter the excretion of this acid falls, lactic acid excretion remaining little changed. As pyruvic acid excretion decreases, urinary volume becomes greater, and the pH of the urine increases. Since pyruvic acid is an intermediate product of the anaerobic or aerobic metabolism of carbohydrate, Räihä believes its presence in the urine of full-term infants indicates a fault or strain in carbohydrate utilization for energy, possibly resulting from relative anoxia in the tissues during the neonatal period. Such a background is even more likely to obtain under the metabolic conditions of prematurely born infants, and it may well be that the excess of organic acid found in the plasma and urine of those subjects will be identified as arising in this way.

CLINICAL SUMMARY

The available data indicate that although the kidneys perform their work adequately enough for ordinary purposes during neo-

natal life, they probably lack reserve capacity for meeting abnormal situations. The major elements in this state of affairs have been shown to be the following:

1. *Renal immaturity*, which, by histological evidence, occurs until about the 35th week after conception, whether all of this period is spent *in utero* or not.

2. *Decreased function*, as judged by urea clearance (and by clearance of electrolytes from the blood as well); most evident in tests upon prematures but apparently persisting, in a diminishing degree, well into infancy.

3. *Limitation of water* available for urinary excretion, with average urinary volumes of only 15–16 cc. in the first 24 hours, 58 cc. on the third day, and nearly 200 cc. on the sixth day.

4. *Low concentration of urinary solids* throughout the newborn period.

5. *Albuminuria* occurring in the majority of newborn infants, with a particular prevalence in the urine of young prematures.

6. A period of *post-natal weight loss*, largely dehydrational, amounting to 6 to 10% of body weight during the first 3 or 4 days.

7. In spite of all these factors, a remarkable *stability of sodium and total base* in the plasma, and a slight increase in chloride ions especially during the weight loss period.

8. A blood *hydrogen ion concentration of essentially normal value* with pH averaging 7.4, attained by compensation for a metabolic acidosis. The average blood carbon dioxide content of 49 volumes% (bicarbonate ion 22.1 meq./L) is low largely because of the increase of inorganic and, probably, organic acids in the blood.

Thus newborn infants approach the border of renal inadequacy in so far as preserving a sufficiently normal osmotic equilibrium of water and salts in the body is concerned, but may be still nearer the verge of electrolyte imbalance from the accumulation of organic and other acids. Although the organic acids are not the ordinary ketones, their increased presence may arise from improperly adjusted carbohydrate metabolism. They are normally present in much greater concentration in premature than in full-term infants, so that significant "acidosis" is a much more real threat to prematures.

Because of these physiological peculiarities, the physician should note that dehydration is not to be overlooked as completely normal and harmless, nor on the other hand to be overcorrected by the too frequent or lavish use of salt solutions hypodermically. Edema is easily produced by this means, and, indeed, it not uncommonly occurs spontaneously during the newborn period. If the kidneys

are already faced with some difficulties in the way of excreting salt, to add any excess of electrolytes is obviously an error. Guidance will be gained from inspection of the temperature and weight chart, and particularly of the baby itself, for a satisfactory weight chart may actually mean an edematous infant. Albuminuria and mild azotemia cannot necessarily be taken as signs of abnormality. Should the infant still be losing weight after the fourth day, particularly if the temperature is above normal, and should inspection show evident dehydration, from 10 to 15 cc. of normal salt solution per pound may be given hypodermically. Larger amounts will of course be needed if abnormal fluid losses, such as from diarrhea or vomiting, are occurring. Under such conditions, especially in premature infants, measurement of blood bicarbonate (or CO_2 combining power) usually shows an unexpectedly marked shift toward an acidosis which will require the prompt use of lactate or bicarbonate and glucose solutions for its correction.

BIBLIOGRAPHY

1. WINDLE, W. F.: Physiology of the Fetus; Origin and Extent of Function in Prenatal Life, Philadelphia, W. B. Saunders Company, 1940.
2. MAKEPEACE, A. W., FREMONT-SMITH, F., DAILEY, M. E., and CARROLL, M. P.: Nature of amniotic fluid; comparative study of human amniotic fluid and maternal serum, Surg., Gynec. & Obst. 53: 635, 1931.
3. ZANGEMEISTER, W., and MEISSEL, T.: Vergleichende Untersuchungen über mütterliches und kindliches Blut und Fruchtwasser nebst Bemerkungen über die fötale Harnsekretion, München. med. Wchnschr. 50: 673, 1903.
4. TAUSCH, M.: Der Fetalharn, Arch. f. Gynäk 162: 217, 1936.
5. POTTER, E. L., and THIERSTEIN, S. T.: Glomerular development in kidney as index of fetal maturity, J. Pediat. 22: 695, 1943.
6. GRUENWALD, P., and POPPER, H.: Histogenesis and physiology of renal glomerulus in early post-natal life: histological examinations, J. Urol. 43: 452, 1940.
7. McCANCE, R. A., and YOUNG, W. F.: Secretion of urine by newborn infants, J. Physiol. 99: 265, 1941.
8. YOUNG, W. F., HALLUM, J. L., and McCANCE, R. A.: Secretion of urine by premature infants, Arch. Dis. Childhood 16: 243, 1941.
9. GORDON, H. H., HARRISON, H. E., and McNAMARA, H.: Urea clearance of young premature and full-term infants, J. Clin. Investigation 21: 499, 1942.
10. GAMBLE, J. L., and SMITH, C. A.: Unpublished data.
11. ROTT, F.: Beitrag zur Wesensklärung der physiologischen Gewichtsabnahme des Neugeborenen, Ztschr. f. Kinderh. 1: 43, 1910.
12. BAKWIN, H.: Dehydration in newborn, Am. J. Dis. Child. 24: 497, 1922.
13. RUSZ, E.: Die physiologischen

- Schwankungen der Refraktion und Viskosität des Säuglingsblutes, *Monatschr. f. Kinderh.* 10: 360, 1912.
14. SALGE, B.: Die physikalischen Erscheinungen des Blutes beim gesunden und kranken Säugling, *Ztschr. f. Kinderh.* 1: 126, 1911.
 15. ROMINGER, E.: Über den Wassergehalt des Blutes des gesunden und ernährungsgestörten Säuglings, *Ztschr. f. Kinderh.* 26: 23, 1920.
 16. LUST, F.: Über den Wassergehalt des Blutes und sein Verhalten bei den Ernährungsstörungen der Säuglinge, *Jahrb. f. Kinderh.* 73: 85, 179, 1911.
 17. HAMILTON, B., and DEWAR, M. M.: Relation between water and dry substance in body of rat before and after birth, *Growth* 2: 13, 1938.
 18. FEHLING, H.: Beiträge zur Physiologie des placentaren Stoffverkehrs, *Arch. f. Gynäk.* 11: 523, 1877.
 19. CAMERER, W., and SÖLDNER: Die Chemische Zusammensetzung des Neugeborenen, *Ztschr. f. Biol.* 39: 173, & 40: 529, 1900.
 20. FELDMAN, W. M.: *The Principles of Ante-natal and Post-natal Child Physiology Pure and Applied*, London, Longmans, Green & Company, 1920.
 21. GUNDOBIN, N.: *Die Besonderheiten des Kindesalters*, Berlin, S. Rubinstein, 1921.
 22. HELLER, F.: Die Albuminurie neugeborener Kinder, *Ztschr. f. Kinderh.* 7: 303, 1913.
 23. FRANZ, T., and VON REUSS, A.: Beiträge zur Kenntnis des Harnes in den ersten Lebenstage, *Ztschr. f. Kinderh.* 11: 193, 1914.
 24. EWALD, L.: Studien über Albuminurie bei Neugeborenen, *Monatschr. f. Geburtsh. u. Gynäk.* 43: 347, 1916.
 25. PFAUNDLER, M. V.: Physiologie, Ernährung und Pflege des Neugeborenen, einschliesslich des Lebensschwachen, in Döderlein, A.: *Handbuch der Geburtshilfe*, Vol. 1, München, J. F. Bergmann, 1924.
 26. SALMI, T.: Untersuchungen über den Blutdruck und den Reststickstoff des Blutes beim Neugeborenen, mit besonderer Berücksichtigung der Kinder von Nierengestosemüttern, *Acta paediat.* 18: 92, 1935.
 27. BRUCH, H., and McCUNE, D. J.: Involution of adrenal glands in newly born infants, *Am. J. Dis. Child.* 52: 863, 1936.
 28. HOAG, L. A., and KISER, W. H., Jr.: Acid-base equilibrium of new-born infants; normal standards *Am. J. Dis. Child.* 41: 1054, 1931.
 29. MARPLES, E., and LIPPARD, V. W.: Acid-base balance of new-born infants; consideration of low alkaline reserve of normal new-born infants, *Am. J. Dis. Child.* 44: 31, 1932.
 30. MARPLES, E., and LIPPARD, V. W.: Acid-base balance of new-born infants; influence of cow's milk on acid-base balance of blood of new-born infants, *Am. J. Dis. Child.* 45: 294, 1933.
 31. LIPPARD, V. W., and MARPLES, E.: Acid-base balance of new-born infants; effect of ingestion of alkali on acid-base balance of new-born infants, *Am. J. Dis. Child.* 46: 495, 1933.
 32. MILLER, R. A.: Shock in the new-born infant, *Arch. Dis. Childhood* 16: 230, 1941.
 33. EDELSTEIN, F., and YLLPÖ, A.: Übergang der sogenannten dif-

- fusiblen Serumsalze durch die Placenta, *Ztschr. f. Kinderh.* 27: 79, 1920.
34. KOTIKOFF, J. A.: Über den Mineralgehalt im Blute der Kinder im ersten Lebensjahr, *Jahrb. f. Kinderh.* 138: 280, 1933.
35. VOLLMER, H.: Der Chlorspiegel des Neugeborenenblutes in seinen Beziehungen zum transitorischen Fieber, *Ztschr. f. Kinderh.* 37: 252, 1924.
36. BRANNING, W. S.: Acid-base balance of premature infants, *J. Clin. Investigation* 21: 101, 1942.
37. GAMBLE, J. L.: *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*, Boston, Harvard Medical School, 1942.
38. YLLPÖ, A.: Neugeborenen-, Hunger-, und Intoxikationsacidosis in ihren Beziehungen zueinander, *Ztschr. f. Kinderh.* 14: 268, 1916.
39. YLLPÖ, A.: Beitrag zur Azidosis bei Neugeborenen, *Acta paediat.* 3: 235, 1924.
40. RÄIHÄ, C. E.: Über einige Neugeborenenprobleme (vorläufige Mitteilung), *Acta paediat.* 28: 390, 1941.

Chapter XII

NEONATAL ENDOCRINOLOGY

Section 1 . . . The Sex Hormones

Section 2 . . . The Adrenal, Thyroid, Pancreatic, and Parathyroid Hormones

Section 3 . . . Clinical Summary

THE SEX HORMONES

WHEN ONE CONSIDERS the quantitative and qualitative alterations in sex hormone production by the maternal organism during pregnancy, and the length of time during which the fetus has been living in this milieu, it is not surprising that the most evident endocrinological peculiarities of the newborn infant show themselves in the sex organs. To describe these manifestations is not difficult, but to present an exact account of their etiology in full detail is not yet possible.

The newborn female baby shows characteristic gross and microscopic alterations of the external genitals. These parts are swollen, moist, and congested, often with sufficient prominence of the labiae, the clitoris, and the glans clitoritidis, as almost to suggest a pseudo-hermaphroditism. Small tags or excrescences occasionally appear, particularly about the inner surfaces of the labiae, and sometimes with such prominence as to indicate a need for subsequent surgical removal—which never becomes necessary. During the first week after birth the region exudes a discharge at first thin and glairy, then thicker and milky white or even yellow. By the seventh to the fourteenth day the discharge usually has disappeared or become much less evident, and any tags of prominently swollen tissue have shrunk to blend with the normal contour, but a certain generalized enlargement may be evident for a month or more. These local alterations are evident in prematurely born infants as well as in those born at term. At about the seventh day an occasional full-term baby may show a little blood in the vaginal discharge; although commonly called “vaginal” bleeding, the source of such blood has been shown to be endometrial.

Microscopic and chemical investigations, most fully presented by Fraenkel and Papanicolaou¹ and by Dobszay,² have revealed the finer details of these transitory phenomena. In both premature and

mature infants a multilayered hypertrophy of the vaginal epithelium is present at birth; within 48 to 60 hours thereafter a progressive desquamation of these squamous cells is well under way, and the epithelium takes on an appearance of increasing atrophy and inactivity by contrast to its former cellular status. After the third week the vaginal epithelium has usually attained its normal infantile appearance. Coincident with these post-natal histologic alterations are a local bacterial flora and chemical reaction quite unlike those of subsequent infancy and childhood, but similar to those appearing under the influence of estrogenic hormones in later life. The vaginal epithelium of newly born girls contains considerable glycogen,² which, in parallel with the other manifestations, soon decreases and disappears not to reappear until after childhood. The uterus is at first large and congested, and there is reason to believe that its cervical canal is more definitely patent during the neonatal period than immediately thereafter.²

The ovaries of the newborn infant sometimes show the follicular ripening and luteinizing effects associated in experimental animals with the gonadotropic effect of injections of pregnancy urine or anterior pituitary hormone. This appearance of the ovaries is more consistently encountered in the full-term infant than the premature, which suggests the action of a substance or stimulus provided for a longer period or in greater concentration when full gestational life has occurred than when it is prematurely interrupted.

Examination of the prostate has shown that the male fetus or newborn infant displays certain peculiarities suggestively analogous to those of the newborn female. These are of two types: the one manifestation occurs in all male fetuses from about the fifth month of gestation until birth and for a few days thereafter, the other appears only in fetuses and infants at complete or nearly complete gestation.³ The first is a squamous metaplasia of the epithelium, especially that of the utricle, prostatic urethra, and prostatic glands. As fetal development advances, the metaplasia results in a localized hypertrophy sometimes distending the utricle enough to cause some obstruction to urinary flow through the prostatic urethra. It is noteworthy that the portions of the prostate showing this metaplasia (and ridding themselves of it by desquamation during the first weeks after birth) are the anatomical homologues of the vaginal structures more or less similarly involved in the female. The second prostatic alteration, observed only at full development, is a focal hyperplasia of occasional portions of the acinar epithelium, suggestive of scattered secretory activity. Moore,⁴ who also described this phenomenon, was likewise struck

by its absence from the prostates of premature fetuses and infants. Both the squamous metaplasia of the prostate and the focal secretory hyperplasia normally undergo regressive changes during the neonatal period.

As though to prove that these alterations in the specific female and male genital organs arise from a common cause, infants of either sex display a further neonatal alteration in the one more or less sexual tissue they share—the mammary glands. It is well known that soon after birth there appears an enlargement of the breasts, the so-called (and miscalled) “neonatal mastitis”; and it is a matter of common knowledge and superstition that a small amount of secretion may be formed, the “witches’ milk” or *hexenmilch*.

Joseph⁵ stated that breast enlargement occurred in all but 5 per cent of a series of newborn infants he studied, and that secretion took place in from 80 to 90 per cent of all those with enlargement. But the recent and larger investigations of Forssell⁶ indicate that actual mammary secretion must be a practically universal attribute of neonatal life. His findings deserve presentation in some detail. From observation of something over a thousand subjects he concluded that some “witches’ milk” is formed by 99 per cent of full-term infants but by only 50 per cent of premature ones. Indeed lactation was found in only one of 17 infants weighing less than 1600 grams ($3\frac{1}{2}$ lb.) at birth. No effect whatever could be assigned to the infant’s sex. Lactation was seldom noted as soon as the baby was born, but in Forssell’s experience first appeared most commonly on the third day, with onset on the fourth, second, fifth, and first days occurring in order of diminishing frequency. Lactation on the first day was associated with greater birth weight, as was more prolonged duration of the process. In few infants did secretion begin after the eighth day; nevertheless an onset after the age of three weeks was twice observed. The somewhat surprising observation was made that 75 per cent of the subjects still had occasional secretion at 3 or 4 months of age. In no way can the amount or duration of the lactating process in the infant be correlated with that in the mother, although chemical studies of the neonatal mammary secretion have shown it to be much like ordinary colostrum.⁷

While a close parallel is traceable between the events in the newborn and the general changes incidental to pregnancy and the puerperium in the mother’s body,^{8,9,10} and while there are suggestive differences between the manifestations of premature and full-term infants, many controversial points exist in regard to the underlying etiological mechanisms. Some of these arise from the fact that the

sources and the specific activities of maternal hormones themselves are not yet completely understood. Arguments have arisen over the exact parts played by several supposedly individual hormones secreted by the mother's ovaries and hypophysis, and by the placenta; the facility with which these cross the placenta to the infant has not been entirely established; the role of the infant's own internal secretions is not yet determined. Out of a rather confused literature several items emerge:

1. All of the local changes in the genital organs of newborn female infants can be imitated or produced experimentally by the parenteral administration of estrogens to newborn animals or to human infants slightly past the neonatal periods.^{2,11,12} The account given by Dobszay describes genital swelling, epithelial alteration, vaginal discharge, change in bacterial flora, cellular glycogen content, uterine enlargement with patulence of the cervical canal, and mammary hypertrophy, all experimentally brought about at will in this manner. Sharpey-Schafer and Zuckermann¹² administered estradiol to two male infants (with fatal congenital deformities) during a seven weeks' period, and demonstrated thereafter the persistence of those changes characteristic of the neonatal prostate which should have undergone involution under ordinary circumstances.

2. Biologic tests have shown an excess of estrogens in the blood of male and female infants at birth,^{5,11,13-15} which correlated closely with the concentration of the same substances in the maternal blood. Although some evidence¹⁵ suggests an actually greater amount in the infant's circulation than in the mother's, the recent work of Sklow¹⁶ has shown the measurable estrogens of the former to be about 70 per cent as great as those of the latter. An excretory tide of estrogens appears in the infant's urine during the first week after birth⁹⁻¹¹ and diminishes toward the end of this period.

3. Maternal lactation is supposedly the culminative response to three essential hormone activities: (a) breast growth from estrogen activity, (b) proliferation of secretory tissue from luteal hormones (progestins) formed in the corpus luteum and placenta, and finally (c) actual secretion from pituitary prolactin (mammatropin, lactogen). However, lactation has been artificially induced in infants past the newborn period by the successive exhibition of the first and third of these principles only.² There is somewhat less information concerning the presence and amount of corpus luteum hormones and of the pregnancy gonadotropin (anterior pituitary-like substance—Collip) in the newborn infant, than is available concerning estrogens. In experimental rabbits and cats the pituitary gonado-

tropic hormones and the anterior pituitary-like substance of pregnancy urine seem unable to pass the placenta in either direction,^{17,18} but their activity has been demonstrated to some degree in the fetal fluids and neonatal blood of human subjects.^{11,13,16,19}

4. Prolactin does appear in the urine of infants before and during the period of their lactation, and in amounts more or less proportional to the degree of mammary secretion.²⁰ The source of this hormone (whether fetal or maternal) is under some dispute. Bates, Riddle, and Lahr²¹ have found an excessive amount of prolactin in the pituitaries of embryo calves, but this was not confirmed by other investigators.²² From the evidence of Bates and his colleagues,²¹ Nelson²³ maintains that the mammary glands of human infants secrete because the formation of prolactin in their own pituitary glands is excessive both before and after birth, and that the "witches' milk" disappears not from exhaustion of maternal prolactin recently supplied in excess, but from the absence of any such mechanical stimuli as the regular emptying of the infant's breasts.

5. The indubitably large amount of estrogen in the newborn infant's body is usually assumed to be of placental or transplacental origin. However, Parker and Tenney,²⁴ having observed that pregnant women exhibit a decline in estrogen excretion if the fetus dies but placental tissue survives *in utero*, have made interesting analyses of various maternal and fetal organs for their estrogen content. The results indicate the inadequacy of available data for final deductions, for, in gravid women dying suddenly, the maternal and fetal liver tissues showed actually greater concentrations of estrogens than did the corresponding placentas. The fetal adrenals, and sometimes the kidneys also, showed more estrogens than were present in the placenta. Thus, unless estrogen is accumulated by a storage process in these and other organs of the fetus, it may be that before and at birth some general system in the fetus and newborn is engaged in active estrogen manufacture. Parker and Tenney²⁴ have tentatively proposed that the cells engaged in cholesterol metabolism might play this role.

To summarize the observations above, it is undeniable that the infant at birth has been exposed to strong and physiologically effective stimulation from endocrine substances relating to the genital organs. To what exact degree these are of exogenous or endogenous origin has not been settled, but the major external evidences of their activity probably depend both upon the presence and the withdrawal of hormones originating in the mother. Since the opportunities of premature infants for exposure to estrogens have

been more or less curtailed, such subjects show somewhat modified responses. It is not surprising that attempts have been made to offer premature infants whatever benefits might conceivably accrue from post-natal treatment with various female sex hormones during some of the period they would normally have spent *in utero*. Certain German workers have been enthusiastic over results following the feeding or injection of colostrum, maternal serum, pituitary gonadotropic hormone, and estrogens from the ovary.²⁵⁻²⁷ Data have been published to show that while every one of these procedures had a salutary effect on the post-natal weight change of prematures, the injection of purified hormones was the most striking in its result. Moncrieff²⁸ observed rather less effect in infants treated with estrogen during the first 8 days of life. There is indeed no more reason to assume that the neonatal phenomena normally brought about by all these mechanisms are any more necessary or valuable for the infant's progress than are many other after-effects of intra-uterine environment such as icterus neonatorum.

All that has been said above has to do with processes affecting newborn babies of either sex. How the developmental integrity of the infant's own sexual organs and their cells is protected from abnormality in the unusual hormonal environment provided by the pregnant mother is the subject of interesting speculation and experiment. It has recently been shown that the male animal fetus *in utero* can be feminized or the female one masculinized by treatment of the mother with large and properly timed doses of estrogens and androgens respectively.²⁹ In maternal animals sufficiently treated with estrogens to feminize the male, the female offspring of the same litter show genital malformations and growth arrests. The resultant warping of genital development appears to be a permanent one, not straightening out as the altered young develop into mature animals. Such experiments hint that during fetal life and perhaps in early post-natal existence, there may be some mechanism which acts as a protection against the untoward effect of an unopposed tidal wave of maternal estrogens. Burrows and others³⁰ examined the urine of a group of women throughout their pregnancies to see whether those ultimately giving birth to male infants excreted any greater amount of androgen than did the others. Although the range of results was wide and the statistical significance dubious, the excretion averaged 26.2 (mgm. ketosteroid per liter) in mothers of males, as compared to 14.6 in those of females. It is interesting that all the higher ketosteroid values encountered were at about the third month, since it has been shown that animal fetuses are not "intersexed" by hormone injections unless these are

given the mother early in the gestation period. Until this work is substantiated it is not essential that the source of extra androgen excretion be identified, but the fetal gonads or adrenal cortex suggest themselves as possibilities. Assays for androgens in human placentas at term have shown a slight difference in favor of those of male infants.³¹

THE ADRENAL, THYROID, PANCREATIC, AND PARATHYROID HORMONES

The **adrenal glands** of the newborn present a picture strikingly different from their appearance in later life. During fetal growth the glands are of relatively large size;³² this enlargement becomes so great that they represent 0.2 per cent of the entire body weight at birth, and thus have about 20 times their relative size in the adult. The enlargement is due to a specially developed and promptly abandoned zone of cells lying inside the layers composing the true cortex, and variously called the fetal cortex, the X-zone, the boundary zone, the embryonic zone, and the androgenic zone or tissue. The latter term is used by Grollman³³ but the term "fetal cortex" may be preferable since evidence conclusively proving an androgenic function is still wanting.

The involution of the fetal cortex begins within 3 or 4 days after delivery but occasionally is under way at birth,³⁴ and proceeds by vacuolization until a rather poorly defined completion at an age variously observed to be from 2 weeks to 1 year.³⁴⁻³⁸ It is probably true that the major stages of involution are over by the end of the fourteenth day and it is certain that the most active involution is to be observed during the second week. Since the cells thus discarded appear early in fetal life, they are evident in the adrenals of infants born prematurely, although somewhat less completely developed than in infants of full term;³⁴ the involution of the fetal cortex proceeds as rapidly in the premature as in the full-term infant.³⁶ There seems to be no difference depending upon the child's sex. The phenomenon is apparently demonstrable in monkeys, but peculiar differences in this regard are shown by the various species of lower mammals, in some of which a homologous tissue or its involution has not been demonstrated.³³ In the mouse the involution process, although quite definite, takes place much later in females than in males.³⁹

Much confusion has arisen through experiments designed to demonstrate the maternal-fetal adrenal cortical hormone relationship and interpreted without proper regard to the peculiarities of this fetal cortical tissue. Whatever function this zone of cells serves,

it is almost certainly not the same as that served by the adrenal cortex in later life. Therefore, before discussing the activities ordinarily associated with adrenal cortical hormone, something may be said of the observations and beliefs regarding the independent function of the fetal cortical tissue. Grollman,³³ Broster,⁴⁰ Benner³⁴ and others have assumed that it is an androgenic tissue, identical with that which overgrows or overpersists in the clinical conditions known as the "adreno-genital syndrome" and "adrenal virilism" which are occasionally seen in children, adolescents, and adults. The flooding of the fetus with estrogenic substance *in utero* is, according to this theory, thus prevented from exercising a feminizing effect, and a balance is preserved within which the fetal sexual development can proceed properly. It is known that adrenal cortical enlargement of unusual degree is frequently found in pseudo-hermaphroditic infants.^{33,41} However, attempts to demonstrate an androgenic activity in the fetal cortex of animals, or to extract androgenically potent substances from these cells in human infants, have given negative results.^{42,43} The effectiveness of the methods used was not always checked by parallel observations made with the androgenic tissue from cases of adrenal virilism, but it is known that the adrenals in virilism do have an extractable principle of an androgenic nature. The 17-ketosteroid excretion is definitely increased in the urine from older children with adrenal virilism, but no elevation of the urinary concentration of these substances has been found in normal newborn infants.⁴⁴ Still, the andromimetic theory has more to recommend it than other hypotheses that the fetal cortex and its involution are in some way related to the alterations in oxygen tension, heat exchange, or regulation of respiration, coincidental to birth.

Benner,³⁴ who has given the most recent account of the behavior of the "true" cortex while the fetal cortex is undergoing its involutions, states that the former zone widens reciprocally with the disappearance of the latter one. By the first month after birth the true cortical tissue has increased to two or three times its size at birth but, of course, never attains the width earlier occupied by the fetal cortex. Thus the neonatal period is a time of regression of cells whose function is poorly understood but extension of others whose effects should be more easily interpreted. In an attempt to throw light upon the significance of the involution process, which might perhaps serve as well to illuminate the results of true cortex evolution, Bruch and McCune³⁸ have made most welcome measurements of several substances usually reflecting alterations of adrenal cortical hormone. The averages of their measurements (Figure 35),

made upon the blood of a large number of subjects aged from the moment of birth to the 25th day of life, show surprisingly steady levels of sodium, total base, and other substances, and offer no testimony to any inaccuracy of adrenal cortical control during this period of sweeping change in adrenal cortical morphology.

Passage of the adrenal cortical hormone across the placenta from fetus to mother, or in the reverse direction, has seemingly occurred in some animal experiments but not in others.^{34,45-47} During late pregnancy some alleviation of cortical deficiency symptoms seems to occur in the adrenalectomized bitch, with a typical Addisonian crisis after the pups are born.⁴⁸ The placental permeability for adrenal medullary secretion is also in some dispute.^{47,49-51} In the majority of experiments the results suggest that passage from fetus to mother is possible. Adrenalin is said to occur in the urine and blood of infants whether prematurely born or delivered at term, though, according to Macchiarulo,⁵² in somewhat lower concentration than in the blood of their mothers. Whereas adrenalin is locally demonstrable in the adrenal medulla of animal fetuses, the human fetal medulla seems almost completely without its presence. Windle³² quotes some evidence to show that a fetal or neonatal deficiency in this respect may be compensated for by adrenalin formed in other chromaffin tissue, such as the aortic paraganglia.

On rather empirical grounds, adrenal cortical hormone has been therapeutically administered to newborn infants.⁵³ The resultant slight reduction of post-natal weight loss does not necessarily prove a neonatal deficiency of this hormone, for observations⁵⁴ have shown that such medication causes a retention of water and a corresponding gain in weight in quite normal adult subjects.

The morphology of the human **thyroid gland** at birth is the result of an orderly fetal growth and differentiation. An arrangement of secretory cells into irregular vesicles appears at three or four months of gestation; by six months some storage of glandular secretion as colloid appears in occasional vesicles, and by the eighth or ninth month in most of them.⁵⁵ Sections of the gland taken at birth and especially a few days thereafter show a lessened amount of retained colloid, practically all of the vesicles having become empty and presenting some desquamation of occasional epithelial cells into their lumina. There is also considerable hyperemia in such glands.⁵⁵⁻⁵⁸ This immediately postnatal period is then followed by a gradual reaccumulation of colloid reserves. All this suggests a glandular tissue engaged in active function during gestational growth and passing through a period subsequent to birth during which the current secretion is insufficient for the body's

needs, so that reserves are drawn upon. Most physiological observations are in accord with this assumption.

Evidence from amphibian larvae, the embryos of birds, and the fetuses of animals and man shows that the biologic activity of thyroid cells appears early, and perhaps before they have arrived at their vesicular arrangement in the gland. Radio-active iodine is fixed, probably as thyroglobulin, in the thyroids of tadpoles of 10 mm. length.⁵⁹ In the human and the animal embryo, iodine is concentrated in the thyroid by the end of the first third of development.^{32,60} Thyroxine has been demonstrated in the human embryo at the third month.^{61,62} By the end of human fetal life the percentage of iodine present as thyroxine iodine is not different from the corresponding figure for the adult thyroid;⁶² the actual amount of late fetal thyroxine is low, but it has been pointed out that the metabolic requirements of the fetus are not very great. Although there have been negative reports,⁶³ the gland seems to have demonstrable biologic function by the middle of gestation, for at this time tissue transplants show specific accelerative effects upon growth when engrafted into amphibian larvae.³² Thus the human organism seems able to provide its own thyroid hormone for some time before birth, and probably does so independently of the maternal thyroid.

Nevertheless, much clinical observation has indicated that under some circumstances the placenta is able to transmit thyroid hormone either from the mother to the fetus or in the reverse direction. In the congenitally hypothyroid or athyrotic infant, cretinoid characteristics make their first appearance only some weeks after birth. Wagner-Juaregg⁶⁴ has reported the case of a Swiss woman who bore a succession of such infants until treatment with thyroid substance was instituted during a subsequent pregnancy with the result that a normal infant with no later signs of hypothyroidism was then born. The case has also been reported⁶⁵ of a myxedematous woman whose symptoms and requirement for thyroxine medication underwent an obvious remission during pregnancy, only to recur soon after she had been delivered of a normal infant. Thus hypothyroid states of either the fetus or the mother appear to be masked so long as the placenta provides a channel by which thyroid hormone can be brought from the associated organism. That any rapid and unimpeded transplacental flow of this substance takes place seems somewhat doubtful in view of the simultaneous measurements of thyroid hormone iodine made by McClendon and McLennan.⁶⁶ Samples obtained by them at human birth showed the concentration to be usually less in the umbilical than in the ma-

ternal circulation, and sometimes this difference was so great that the cord blood contained less than half the amount of hormone iodine simultaneously present in the blood of the mother.

Variation in the development of the fetal thyroid and in its size and function at birth may be brought about by an inadequacy of iodine in the maternal diet. The thyroids of infants born in "goiter regions" where dietary consumption of iodine is low show a definite tendency to enlargement.⁵⁷ Similar changes were accurately reproduced by Marine⁶⁷ in experiments with the offspring of partially thyroidectomized dogs. Successive litters of pups could be made either normal or goiterous by the withholding or administration of small amounts of iodine in the maternal diet.

No data directly revealing the status of thyroid activity during the human neonatal period have appeared in the literature. The basal metabolism has been shown to be low at birth and to increase slightly during the first month of extra-uterine life (see Chapter VII). Perhaps in keeping with this are the implications of measurements of blood iodine in infants and children.⁶⁸ These have shown somewhat lower amounts of iodine in samples taken during the first 24 hours after birth than in those taken in the later age periods from 2 days to 13 years. The average for the first day was 4.7 micrograms; for the remainder of infancy and childhood 6.6 micrograms. Although the ranges were from 1 to 11 micrograms in the former group and from 3 to 12 in the latter, so that a wide overlap occurred, almost all successive measurements from the same infant during neonatal period showed a tendency to increase. Since many workers have shown that the blood iodine concentration reflects—though rather broadly—the activity of thyroid secretion, these figures bear out the impression that thyroid function may be somewhat less than adequate at birth, with a definite improvement shortly thereafter. As with most other hormones, thyroid substance has been administered to premature infants in the hope that some beneficial effect might result from the alleviation of a possible inadequacy of glandular secretion. Such infants showed a slightly lower mortality than untreated controls; although treated infants tended to gain weight more slowly, they seemed more active and less difficult to feed and to keep warm.⁶⁹ The degree of these changes was not sufficiently striking to warrant a belief that premature birth is associated with any serious deficiency of thyroid activity.

The pancreas of the fetus has been most extensively studied by Nakamura⁷⁰ who compared the relative proportion of islet tissue before and after birth with the status obtaining in later life. In general his researches indicate a fetal and neonatal excess in the

number of cells associated with insulin formation; these islet cells sometimes occurred with four times the frequency usually encountered in sections of the pancreas from older subjects. In keeping with this is the fact that more insulin can be extracted per gram of fetal calf pancreas than from the same tissue of cattle at any other age.⁷¹ Moreover the amount of insulin has been shown to be twice as high in specimens obtained at 6 to 8 weeks after birth than in those obtained at 2 years. These findings are based on the amount per unit of pancreas. Indeed it will be recalled that insulin was first prepared from fetal pancreatic tissue. In keeping with these observations, the glucose concentration in the human umbilical cord blood at birth is lower than that in the maternal blood, and the blood sugar level in the neonatal period after premature or full-term birth usually tends to be lower than later in childhood (see Chapter IX).

There is much to indicate that besides a potentiality for considerable insulin secretion, the fetus and newborn may have an unusual tolerance or resistance to the action of that substance and to such hypoglycemia as it may induce.⁷² Thus Schlossmann⁷³ has stated that injections of more than 700 units of insulin into fetal dogs neither lowered their blood sugar beyond 40 mgm. per cent nor produced convulsive movements suggesting sensitivity to hypoglycemia. Although sheep and goats are known to be somewhat insulin resistant at any age, this would scarcely be sufficient to account for the fact that fetuses of those species have tolerated the injection of 1200 units of insulin with a resulting decline in the blood glucose only from 172 to 148 mgm. per cent.⁷⁴ It is probable that under such circumstances some glucose may cross the placenta from the mother's blood to neutralize the effects of insulin in the fetal body, but in all these experiments the maternal blood showed only mild decrease in sugar. In the dog fetus the blood sugar is depressed only slightly below 40 mgm. per cent when large doses of insulin are administered after the umbilical circulation is interrupted. Sensitivity tests in a few newborn human infants have shown a moderate response to insulin.⁸¹ More observations might well be made, particularly upon prematurely born subjects.

A great deal of speculation has arisen over the glucose, insulin, and islet-cell relationships between pregnant women and their offspring both before and after delivery. The obvious significance of such a relationship in maternal diabetes, and the fact that the infants of diabetic women often do manifest unusual symptoms (frequently accompanied by more profound hypoglycemia than that usually observed in the newborn babies of non-diabetic moth-

ers) make the subject one of much practical importance. Interpretation of observations is difficult since both insulin and glucose are available on either side of the placenta, and since the amount of each has an effect on that of the other. In the animals mentioned above, and in rabbits investigated by Snyder and Hoskins⁴⁹ the injection of insulin into the fetus seemed to have little or no effect on the level of glucose in the maternal blood. Pregnant animals rendered diabetic by pancreatectomy have shown no clear-cut and consistent amelioration of symptoms or of insulin requirement which might suggest a response to fetal insulin.⁷⁵⁻⁷⁷

That pregnancy diminishes the insulin requirement of diabetic women has not been regularly demonstrated^{78,79} but beside the possible effect of fetal islet secretion there are obviously other and more far-reaching metabolic factors of pregnancy to be considered in judging the significance of published observations. If insulin itself does not cross the placenta freely, a maternal environment of hypo-insulinism might cause the fetus to respond by an over-development of the islets of Langerhans under the stimulus of an excessive transplacental glycemia. Many observations have connected this possibility with various post-natal symptoms, often of a hypoglycemic nature, shown by the babies of diabetic mothers.^{80,81} The careful studies of Helwig⁸² and of Potter and her associates⁸³ have shown a strong though not consistent tendency toward fetal islet hypertrophy and hyperplasia in many infants born to diabetic mothers. This was especially common in the larger infants investigated. A finding which should lead to some caution in the application of all of these observations has been the presence of islet hypertrophy under other circumstances than maternal diabetes, and its particularly frequent occurrence in infants with erythroblastosis fetalis.⁸³

It seems proper to conclude that the fetus and newborn infant may normally produce a comparatively excessive amount of insulin, but be somewhat insensitive to its action or to the results thereof. The infants of diabetic mothers may or may not exceed others in insulin production; should they do so it appears that this is to be viewed as the result of an excess of glucose reaching them across the placenta. To reason further and view the process as the cause of an amelioration of the maternal diabetic state is not allowable from present evidence.

Little knowledge is available concerning the **parathyroid glands** of the newborn. The degree of their secretion in fetal life and its relationship to maternal parathyroid hormone are difficult to evaluate for the same reasons that conclusions concerning fetal and

maternal insulin are uncertain. As insulin activity is reflected by blood glucose concentration, so parathyroid secretion is inferred from blood calcium levels, but the permeability of the placenta for glucose or calcium introduces a variable factor into interpretation. Parathyroidectomized pregnant animals are not protected from tetany by the presence of their fetuses.⁸² It has been shown by Hoskins and Snyder⁸⁴ that parathyroid hormone injected into the dog fetus produces a definite increase in the fetal blood calcium concentration with only a very minor rise in the maternal calcium. On the other hand the administration of parathyroid hormone to the maternal dog causes much more elevation of maternal blood calcium than fetal. Probably calcium does not move with complete freedom across the placenta as it is ordinarily carried in the fetal blood at a concentration of about 12 mgm. per 100 cc., while the maternal level is about 10 mgm. Since parathyroid hormone injected into the maternal animal causes a rise to 15 mgm. on her side of the placenta, with an accompanying elevation to somewhat less than that level on the fetal side, it is arguable that the transplacental passage of calcium produced this effect rather than that an excess of hormone crossed the placenta. One observation of interest is that the fetal organism may be comparatively insensitive to the stimulus of parathyroid hormone. The dog fetuses injected by Hoskins and Snyder⁸⁴ were able to tolerate about 100 times the experimental dose to which their mothers responded. It would be interesting to know whether a relative insensitivity of the same sort occurred in newborn infants. The difference between the fetal and maternal sensitivity suggests the possible fetal and neonatal resistance to insulin mentioned earlier in this chapter.

Concerning parathyroid secretion in the neonatal period, only a little evidence of an inferential sort is available. This has been assembled by Bakwin⁸⁵ in support of the belief that a physiological hypoparathyroidism may partially explain the occasional symptoms of tetany observed in newborn infants. The argument rests on the facts (a) that whatever maternal hormone might have been available to the fetus is suddenly withdrawn by the separation of birth; (b) that the infant shows an early post-natal decrease in blood calcium concentration; (c) that a reduction in urinary excretion of phosphorus (similar to that occurring in hypoparathyroidism) is demonstrable in the newborn infant; and (d) that the newborn infant develops a still more striking hypocalcemia if phosphorus is ingested, much as does the parathyroid-deficient older subject.

Data regarding the manifold functions of the **pituitary gland**

have not been obtained in sufficient quantity or detail to allow any account of hypophyseal activities during early post-natal life. The few observations^{2,18,47,49,86,87} are almost entirely related to the fetal rather than to the neonatal period, and have largely been from experimental animals rather than human subjects. No anatomical changes in the neonatal gland suggesting outstanding alterations of function have been discovered.^{55,88} The pituitary gland therefore will be omitted from further consideration here—not because it lacks importance in neonatal endocrinology, but because a discussion of its importance would be so completely speculative.

CLINICAL SUMMARY

Such endocrinological questions as may confront the clinician will probably be of three sorts:

1. What latitude of alteration in the generative and mammary tissues of newborn infants may be tolerated as within normal limits and thus not demanding interference?

The answer to the first question can be given briefly. Local changes short of actual congenital malformations are present as the results of sufficient physiological causes, and are completely self-righting. Vulvar swelling and discharge (even though somewhat hemorrhagic), the appearance of small local excrescences, and the changes in the breasts of both sexes, are all conditions requiring no attention. The so-called mastitis may, however, become a true mastitis if interference produces infection and abscess.

2. Do endocrine substances have usefulness in the management or therapy of newborn and premature patients?

From what has been said in this chapter it appears unlikely that the administration of endocrine preparations to premature and other newborn infants will do harm, for this period of life seems to be one of some resistance to the activities of those hormones concerning which there have been quantitative studies. On the other hand, there is no wide acceptance of estrogenic, adrenal cortical, or thyroid hormones as useful adjuvants to the general care of premature babies. The manifold alterations produced in the infant directly or indirectly by the mother's estrogens and other sex-regulating hormones cannot be said to serve any useful purpose which is denied to infants prematurely born. Moreover, there is no present evidence of any important strain upon adrenal or thyroid function in normal newborn life.

3. What abnormalities may be anticipated in the offspring of women with endocrinological disturbances, and how should they be treated?

When the mother is herself the victim of thyroid or insulin deficiency, therapeutic action or, at least, clinical observation may be necessary. It is possible, though unlikely except in regions where goiter is very common, that congenital cretinism may be prevented by the administration of thyroid substance to a hypothyroid mother. The endocrinological status of a mother who has borne such an infant, or one with congenital goiter,⁸⁹ obviously deserves investigation before she becomes pregnant again; in cases where more than one abnormal infant has been born, the need for this becomes imperative. The masking of the signs of cretinism during the first months of life by a temporarily sufficient supply of thyroid hormone from the mother is probably too well known to be emphasized again here.

Infants delivered from diabetic women have displayed a varied group of symptoms not all of which can be assigned to hyper-insulinism.⁹⁰ Nevertheless, the major clinical attack upon this problem must at present be an attempt to regulate the maternal blood sugar levels as narrowly as possible during pregnancy and to be extremely watchful for hypoglycemia in the infant during the first few days after its birth. In estimating the significance of blood glucose determinations (which should be made at birth and at intervals of 4 to 8 hours thereafter) it should be noted that normal infants often show levels as low as 50 mgm. glucose/100 cc., without accompanying symptoms. There can be little harm from the oral or parenteral administration of sugar solutions soon after the birth of the infant, but such treatment should be accompanied by chemical measurements, if at all possible. Otherwise the therapy of a situation as yet incompletely understood may result in still further confusion.

BIBLIOGRAPHY

1. FRAENKEL, L., and PAPANICOLAOU, G. N.: Growth, desquamation and involution of vaginal epithelium of fetuses and children, with consideration of related hormonal factors, *Am. J. Anat.* 62: 427, 1938.
2. DOBSZAY, L.: Hormonal reactions of pregnancy, *Am. J. Dis. Child.* 56: 1280, 1938.
3. BRODY, H., and GOLDMAN, S. F.: Metaplasia of epithelium of prostatic glands, utricle and urethra of fetus and newborn infant, *Arch. Path.* 29: 494, 1940.
4. MOORE, R. A.: Histology of newborn and prepuberal prostate gland, *Anat. Rec.* 66: 1, 1936.
5. JOSEPH, S.: Zur Biologie der Brustdrüse beim Neugeborenen, *Monatschr. f. Geburtsh. u. Gynäk.* 83: 219, 1929.
6. FORSELL, P.: Klinische und histologische Untersuchungen über die sog. Hexenmilchsekretion, mit besonderer Berücksichtigung ihres Verhaltens zum Geburtsgewicht des Kindes, *Acta paediat. (suppl.)* 23: 1, 1938.
7. DAVIES, W. L., and MONCRIEFF,

- A.: Composition of milk from breasts of newlyborn infants, *Biochem. J.* 32: 1238, 1938.
8. HALBAN, Über fötale Menstruation und ihre Bedeutung, *Zentralbl. f. Gynäk.* 28: 1270, 1904.
 9. PHILIPP, E.: Sexualhormone, Placenta und Neugeborenes, *Zentralbl. f. Gynäk.* 53: 2386, 1929.
 10. PHILIPP, E.: Schwangerschaftsveränderungen beim Neugeborenen, *Klin. Wehnschr.* 17: 797, 1938.
 11. BRÜHL, R.: Das Vorkommen von Weiblichem Sexualhormon und Hypophysenvorderlappenhormon im Blute und Urin von Neugeborenen, *Klin. Wehnschr.* 8: 1766, 1929.
 12. SHARPEY-SCHAFER, E. P., and ZUCKERMAN, S.: Effect of oestrogenic stimulation on human prostate at birth, *J. Endocrinol.* 2: 431, 1941.
 13. SOULE, S. D.: Impermeability of placenta to prolactin B, *Am. J. Obst. & Gynec.* 27: 723, 1934.
 14. SOULE, S. D.: Presence of estrogenic hormones in maternal and fetal circulation, *Am. J. Obst. & Gynec.* 35: 309, 1938.
 15. SEIGERT, F., and SCHMIDT-NEUMANN: Der Hormonspiegel im mütterlichen und kindlichen Blut am Ende der Schwangerschaft, *Zentralbl. f. Gynäk.* 54: 1630, 1930.
 16. SKLOW, J.: Is the human placenta permeable to gonadotropic and estrogenic hormones? *Proc. Soc. Exper. Biol. & Med.* 49: 607, 1942.
 17. WISLOCKI, G. B., and SNYDER, F. F.: Note on failure of anterior lobe extract to pass from fetus to mother, *Proc. Soc. Exper. Biol. & Med.* 30: 196, 1932.
 18. GOODMAN, L., and WISLOCKI, G. B.: Note on failure of anterior lobe extract to pass from mother to fetus in rabbits and cats, *Am. J. Physiol.* 106: 323, 1933.
 19. GEIST, S. H., and SPIELMAN, F.: Estimation of anterior pituitary-like hormone in cord blood, *Proc. Soc. Exper. Biol. & Med.* 31: 662, 1934.
 20. LYONS, W. R.: Hormone basis for "witches' milk," *Proc. Soc. Exper. Biol. & Med.* 37: 207, 1937.
 21. BATES, R. W., RIDDLE, O., and LAHR, E. L.: Assay of 3 hormones present in anterior pituitaries of 7 types of cattle classified for age, sex, and stage of reproduction, *Am. J. Physiol.* 113: 259, 1935.
 22. (a) REECE, R. P., and TURNER, C. W.: The lactogenic and thyrotropic content of the anterior lobe of the pituitary gland, *Mo. Agr. Exp. Sta. Res. Bull.* 266, 1937.
(b) TURNER, C. W.: Sex and Internal Secretions, ed. by Allen, Danforth, and Doisy, Baltimore, Williams & Wilkins, 1939, p. 776.
 23. NELSON, WARREN O.: Personal communication.
 24. PARKER, F., JR., and TENNEY, B., JR.: Study of estrogenic content of tissues in pregnancy, *Endocrinology* 23: 492, 1938.
 25. SCHILLER, W.: Über die Aufzucht frühgeborener Kinder mit Folliculin, *Arch. f. Gynäk.* 147: 72, 1931.
 26. SCHREIBER: Erfahrungen mit "Unden" bei der Aufzucht der Frühgeburten, *Zentralbl. f. Gynäk.* 57: 1318, 1933.
 27. DAPSY, A.: Ergebnisse der Behandlung Frühgeborener mit Hormon, Colostrum und Schwangerenserum, *Monatschr. f. Kinderh.* 67: 146, 1936.
 28. MONCRIEFF, A.: Value of oestrin for premature babies, *Arch. Dis. Childhood*, 11: 9, 1936.
 29. GREENE, R. R., BURRILL, M. W., and IVY, A. C.: Experimental intersexuality; effect of antenatal

- androgens on sexual development of female rats, *Am. J. Anat.* 65: 415, 1939.
30. BURROWS, H., MACLEOD, D. H., and WARREN, F. L.: Excretion of ketosteroids in human pregnancy urine in relation to sex of foetus, *Nature*, London 149: 300, 1942.
 31. CUNNINGHAM, B., and KUHN, H. H.: Presence of androgens in the placenta, *Proc. Soc. Exper. Biol. & Med.* 48: 314, 1941.
 32. WINDLE, W. F.: *Physiology of the Fetus; Origin and Extent of Function in Prenatal Life*. Philadelphia, W. B. Saunders, 1940.
 33. GROLLMAN, A., *The Adrenals*. Baltimore, Williams & Wilkins, 1936.
 34. BENNER, M. C.: Studies on involution of fetal cortex of adrenal glands, *Am. J. Path.* 16: 787, 1940.
 35. THOMAS, E.: Über die Nebenniere des Kindes und ihre Veränderungen bei Infektionskrankheiten, *Beitr. z. path. Anat. u. z. allg. Path.* 50: 283, 1911.
 36. LEWIS, R. W., and PAPPENHEIMER, A. M.: A study of the involutional changes which occur in the adrenal cortex during infancy, *J. Med. Research* 34: 81, 1916.
 37. SCAMMON, R. E.: The prenatal growth and natal involution of the human suprarenal gland, *Proc. Soc. Exper. Biol. & Med.* 23: 806, 1925-26.
 38. BRUCH, H., and McCUNE, D. J.: Involution of adrenal glands in newly born infants, *Am. J. Dis. Child.* 52: 863, 1936.
 39. HOWARD-MILLER, E.: A transitory zone in the adrenal cortex which shows age and sex relationships, *Am. J. Anat.* 40: 251, 1927.
 40. BROSTER, L. R.: Eight years experience with the adrenal gland, *Arch. Surg.* 34: 761, 1937.
 41. DIJKHUIZEN, R. K., and BEHR, E.: Adrenal hypertrophy in infants; new clinical entity of neonatal period, *Acta paediat.* 27: 279, 1940.
 42. GERSH, I., and GROLLMAN, A.: Relation of adrenal cortex to male reproductive system, *Am. J. Physiol.* 126: 368, 1939.
 43. CARNES, W. H.: Androgenic assay of human fetal adrenal, *Proc. Soc. Exper. Biol. & Med.* 45: 502, 1940.
 44. TALBOT, N. B., and others: Excretion of 17-ketosteroids by normal and by abnormal children, *Am. J. Dis. Child.* 65: 364, 1943.
 45. STEWART, G. N., and ROGOFF, J. M.: Studies on adrenal insufficiency, *Proc. Soc. Exper. Biol. & Med.* 22: 394, 1924-25, and 23: 190, 1925-26.
 46. COREY, E. L.: Survival period in the pregnant and lactating cat following adrenal extirpation, *Proc. Soc. Exper. Biol. & Med.* 25: 167, 1927.
 47. SCHLOSSMANN, H.: Der Stoffaustausch zwischen Mutter und Frucht durch die Placenta, *Ergebn. d. Physiol.* 34: 741, 1932.
 48. BILLMANN, F., and ENGEL, R.: Vikariierender Einsatz fetaler Nebennieren in der Schwangerschaft beim Nebennierenlosen Hund, *Klin. Wehnschr.* 18: 599, 1939.
 49. SNYDER, F. F., and HOSKINS, F. M.: The placental transmission of adrenalin, insulin, and pituitrin, *Anat. Rec.* 35: 23, 1927.
 50. RUPP, H.: Die Durchlässigkeit der Placenta und Eihäute für Antigene, Antikörper und Inkrete, *Arch. f. Gynäk.* 143: 80, 1930.
 51. SCHLOSSMANN, H.: Beiträge zur Biologie der Plazenta. III. Die Durchlässigkeit der Plazenta für Adrenalin, *Arch. f. Exper. Path.* 166: 74, 1932.
 52. MACCHIARULO, O.: Über Adrenalin- und Zuckergehalt des fetalen Blutes, *Arch. f. Gynäk.* 159: 349, 1935.

53. MILLER, R. A.: Desoxycorticosterone acetate and oestradiol di-propionate therapy in new-born infant, *Arch. Dis. Childhood* 16: 113, 1941.
54. CLINTON, M., JR., and THORN, G. W.: Effect of desoxycorticosterone acetate administration on plasma volume and electrolyte balance of normal human subjects, *Bull. Johns Hopkins Hosp.* 72: 255, 1943.
55. COOPER, E. R. A.: *The Histology of the More Important Human Endocrine Organs at Various Ages.* New York, Oxford University Press, 1925.
56. WEGELIN, C.: Schilddrüse: Drüsen mit innerer Sekretion. Vol. 8, *Handbuch der speziellen pathologischen Anatomie und Histologie*; ed. by F. Henke and O. Lubarsch, Berlin, J. Springer, 1926.
57. NEUMANN, H.: Klinische und pathologisch-anatomische Studien zum Problem der Neugeborenen-Schilddrüse, *Arch. f. Gynäk.* 163: 368, 1937.
58. KOCH, F.: Studien über die Morphologie der normalen Schilddrüse; die Schilddrüse der Neugeborenen, *Acta path. et Microbiol. Scandinav.* 15: 198, 1938.
59. GORBMAN, A., and EVANS, H. M.: Correlation of histological differentiation with beginning of function of developing thyroid gland of frog, *Proc. Soc. Exper. Biol. & Med.* 47: 103, 1941.
60. LELKES, Z.: Über den Jodgehalt der fetalen, Neugeborenen- und Säuglingsschilddrüsen, *Endokrinologie* 13: 35, 1933.
61. ELMER, A. W., and SCHEPS, M.: Sur la teneur en thyroxine et en diiodotyrosine de la thyroïde des nouveau-nés et des foetus, *Compt. rend. Soc. de biol.* 118: 1370, 1935.
62. PALMER, W. W., LELAND, J. P., and GUTMAN, A. B.: Microdetermination of thyroxine in thyroid gland of new-born, *J. Biol. Chem.* 125: 615, 1938.
63. NEUWEILER, W.: Über die Funktion der Schilddrüse Neugeborener und der Struma congenita, *Arch. f. Gynäk.* 157: 187, 1934.
64. WAGNER-JAUREGG, J.: Ist das Entstehen des Kretinismus durch intrauterine Behandlung der Frucht zu verhüten? *Schweiz. med. Wchnschr.* 68: 246, 1938.
65. ZONDEK, H.: On problem of foetal function of thyroid gland, *Acta Med. Scandinav.* 103: 251, 1940.
66. MCCLENDON, J. F., and MCLENNAN, C. E.: Hormone iodine in mother's and umbilical cord blood, *Proc. Soc. Exper. Biol. & Med.* 40: 553, 1939.
67. MARINE, D.: The importance of our knowledge of thyroid physiology in the control of thyroid diseases, *Arch. Int. Med.* 32: 811, 1923.
68. FASHENA, G. J.: Study of blood iodine in childhood, *J. Clin. Investigation* 17: 179, 1938.
69. MONCRIEFF, A.: Administration of thyroid gland to premature babies, *Arch. Dis. Childhood* 13: 57, 1938.
70. NAKAMURA, N.: Untersuchungen über das Pankreas bei Föten, Neugeborenen, Kindern und im Pubertätsalter, *Virchows Arch. f. path. Anat.* 253: 286, 1924.
71. FISHER, A. M., and SCOTT, D. A.: The insulin content of the pancreas in cattle of various ages, *J. Biol. Chem.* 106: 305, 1934.
72. HIMWICH, H. E., FAZEKAS, J. F., and HOMBURGER, E.: Effect of hypoglycemia and anoxia on survival period of infant and adult rats and cats, *Endocrinology* 33: 96, 1943.
73. SCHLOSSMANN, H.: Carbohydrate metabolism of foetal dog under influence of insulin, *J. Physiol.* 92: 219, 1938.

74. PASSMORE, R., and SCHLOSSMANN, H.: Effect of large doses of insulin on foetal sheep and goat, *J. Physiol.* 92: 459, 1938.
75. CARLSON, A. J., ORR, J. S., and JONES, W. S.: The absence of sugar in the urine after pancreatectomy in pregnant bitches near term, *J. Biol. Chem.* 17: 19, 1914.
76. ALLEN, F. M.: Experimental studies in diabetes, *Am. J. Physiol.* 54: 451, 1921.
77. MARKOWITZ, J., and SOSKIN, S.: Pancreatic diabetes and pregnancy, *Am. J. Physiol.* 79: 553, 1927.
78. DUNCAN, C. G., and FETTER, F.: The effect of pregnancy on the insulin requirement of the diabetic, *Am. J. M. Sc.* 187: 347, 1934.
79. SMYTH, F. S., and OLNEY, M. B.: Diabetes and pregnancy; observations on offspring with pathologic report, *J. Pediat.* 13: 772, 1938.
80. RANDALL, L. M., and RYNEARSON, E. H.: Delivery and care of new-born infant of diabetic mother, *J. A. M. A.* 107: 919, 1936.
81. HARTMANN, A. F., and JAUDON, J. C.: Hypoglycemia, *J. Pediat.* 11: 1, 1937.
82. HELWIG, E. B.: Hypertrophy and hyperplasia of islands of Langerhans in infants born of diabetic mothers, *Arch. Int. Med.* 65: 221, 1940.
83. POTTER, E. L., SECKEL, H. P. G., and STRYKER, W. A.: Hypertrophy and hyperplasia of islets of Langerhans and fetus and of newborn infant, *Arch. Path.* 31: 467, 1941.
84. (a) HOSKINS, F. M., and SNYDER, F. F.: Calcium content of maternal and foetal blood serum following injection of parathyroid extract in fetuses in utero, *Proc. Soc. Exper. Biol. & Med.* 25: 264, 1928.
- (b) HOSKINS, F. M., and SNYDER, F. F.: Placental transmission of parathyroid extract, *Am. J. Physiol.* 104: 530, 1933.
85. (a) BAKWIN, H.: Tetany in newborn infants; relation to physiologic hypoparathyroidism, *J. Pediat.* 14: 1, 1939.
- (b) BAKWIN, H.: Pathogenesis of tetany of newborn, *Am. J. Dis. Child.* 54: 1211, 1937.
86. CATTANEO, L.: Contributo sperimentale allo studio del passaggio degli ormoni fetali alteravero la placenta, *Ann. di ostet e ginec.* 53: 253 and 407, 1931.
87. HALPERN, S. R.: Quantitative cytological studies of anterior lobe of hypophysis of fetuses and children, correlated with sexual and skeletal development, *Endocrinology* 22: 173, 1938.
88. DAVIES, J. R.: Sporadic congenital obstructive goiter with recovery following operation in 13-day-old infant, *J. Pediat.* 22: 570, 1943.
89. MILLER, H. C., and WILSON, H. M.: Macrosomia, cardiac hypertrophy, erythroblastosis, and hyperplasia of the islands of Langerhans in infants born to diabetic mothers, *J. Pediat.* 23: 251, 1943.

Chapter XIII

NEONATAL IMMUNOLOGY

ALTHOUGH THE SUBJECT of this chapter is outside the territory of physiology, it represents an adjoining field in which the newborn organism presents certain special aspects of behavior. Therefore, just as physiological response to such things as the environmental temperature and the novel requirements of pulmonary respiration and gastrointestinal digestion have been explored earlier in this book, it has seemed desirable to examine the reactions of the newborn infant to infectious agents. Since an exhaustive survey would rapidly lead to considerations far removed from physiology, this has not been attempted; for further information the reader is referred to the reviews by Ssacharoff,¹ Baumgartner,² and McKhann and Kapnick.³

Of the two main approaches to the subject, one concerns *the phenomena which originate from the pre-natal relationship between infant and mother*. The fetus *in utero* has had opportunities for receiving either antigens (such as bacteria and viruses), or antibodies (such as bacterial antitoxins and agglutinins), by passage across the placenta. In response to antigens, the fetus may react with a variety of manifestations including, among others of clinical significance, the active formation of antibodies. Once formed, these can persist more or less indefinitely as influences altering the infant's response to a subsequent experience with the same antigen. When, on the other hand, the factors arriving in the fetal blood are antibodies from the maternal circulation, these can remain after birth for comparatively brief periods of weeks or months, during which they gradually decline in amount, just as does specific antitoxin injected into an individual exposed to diphtheria. Processes of this sort are probably of greater clinical significance and wider variety, and are, perhaps, more clearly understood than those in which the fetus has accepted an antigen from the mother's blood and has been stimulated accordingly to form its own antibody. The other general concept of immunological importance concerns *the inherent capacity of fetal and neonatal tissues to resist infection and to manufacture antibodies*, beyond those which the mother's cells and serum may supply. This concept includes such immunological characteristics as would differentiate the newborn infant from the older subject if the placenta were entirely impervious to antibodies and antigens. It is obvious that constitutional attributes of this

sort are not easy to evaluate during a period in which an indefinite but nevertheless considerable number of passively acquired influences are present in variable amounts. It will therefore be convenient to discuss problems of inherent immunity only after examining the various antigens and antibodies which may be passively acquired, and the effects of their presence.

Infectious agents may reach the fetus either by interference with the normal integrity of the placenta or by penetration without disturbance of its structure. Syphilis and tuberculosis, when acquired *in utero*, involve the placental tissue as well. Whether gonococcal and pneumococcal infections, malaria, and leprosy, reach the newborn infant in the same way is not certain,² for cases, in which the placenta has been thoroughly investigated and the possibility of extra-placental transmission at or immediately after birth has been eliminated, are very few. Probably most infants with neonatal pneumonia or gonococcal infection acquire the organisms from the amniotic fluid or the birth canal. On the other hand, filterable viruses circulating in the maternal blood are undoubtedly able to pass the intact placenta. This is shown by the birth of infants who either present active evidences of measles, chicken pox, smallpox, or other viral diseases, or in whom symptoms develop within so short a period that only an intra-uterine infection could have been responsible. The mother must have the same illness either immediately before or at the time of the infant's delivery.^{2,4} Poliomyelitis does not seem to be transferred from mother to fetus in this way, nor has its virus been obtainable from the spinal cord of an infant born of a mother in the acute stage of the disease.⁵ This is probably because the virus seldom if ever appears in the blood, and thus would not be present in the placental circulation.

Whether infants are sometimes born with antibodies of their own intra-uterine manufacture, lingering after transplacental infection has run its course, is a question of only occasional and academic importance. While there is no theoretical reason that this might not occur, the more probable event would be the death of the fetus. Nevertheless there is evidence for believing that the fetus can form antibodies against antigens acquired passively during procedures calculated to create or enhance active immunity in the pregnant mother. The authors of two recent studies^{6,7} state that mothers immunized to large doses of pertussis vaccine or diphtheria toxoid gave birth to infants whose antibodies were demonstrable over such long post-natal periods as to indicate their active fetal origin through such a mechanism.

Antibodies, as a class, are probably much more easily and fre-

quently acquired by the infant through placental transfer in fetal life than are antigens.⁸ A reason for this is that the non-virus antigens are of larger size than the protein molecules which carry the antibodies. Yet there are differences with regard to antibody transfer which have neither been assignable to molecular size nor explained by any other reason. Diphtheria antitoxin is an example of a highly diffusible antibody present in the umbilical cord blood at birth in concentrations practically equal to those of the maternal blood.^{6,9} The post-natal titer of this antibody declines to become practically absent within three to six months after birth.¹⁰ Tetanus antitoxin also passes the placenta with little hindrance.¹¹ Though less directly measurable than such antitoxins, antibodies against the viruses of measles, chicken pox, mumps, smallpox, and poliomyelitis, if present in the mother's blood, may be relied upon to confer an immunity lasting from 6 to 12 months upon the newborn infant. Most clinical observations suggest a like transfer of relative immunity to the virus causing the common cold, but this neonatal resistance is of brief duration.

The bactericidal antibodies, in contrast to the antitoxic and antiviral substances discussed in the preceding paragraph, usually persist for still shorter periods. Sutliff and Finland,¹² and Fothergill and Wright,¹³ have shown that for a few weeks or months after birth the blood possesses enhanced antibacterial powers against pneumococci and influenza bacilli. Scarlet fever and streptococcal infections generally, are complicated subjects for discussion because of the numerous types of antibodies requiring investigation, but most of them seem to be equally concentrated in maternal and neonatal blood. Thus, the serum of umbilical cord blood will produce local blanching of scarlet fever eruptions, the relative antitoxic activity of the infant's serum in this regard being correlated with that of its mother.¹⁴ Antistreptolysin and streptococcal antifibrinolysin^{15,16} also cross the placenta. Again, most evidence suggests that these streptococcal antibodies disappear somewhat more rapidly from the infant's blood than do the virus antibodies or diphtheria antitoxin. The same abrupt decline characterizes staphylococcal antitoxin (antihemolysin), which is usually as concentrated in the serum at birth as during adult life. By the infant's 4th to 8th week a comparatively minute amount remains.¹⁷ Finally, though this does not completely exhaust the list, typhoid bacillus "H" agglutinins (though not "O" agglutinins) may be found in the newborn infant's blood if they are present in that of the mother.^{2,18} It may be mentioned also that typhoid antigen perhaps crosses the placenta, for the actively produced agglutinins against it have at

least once been demonstrated in the newborn infant without an accompanying transfer of maternal antibody.²

On the other hand, there is abundant clinical proof that under ordinary circumstances no significant resistance to whooping cough is transferred from mother to fetus. Some data indicate a parallelism between the results of complement fixation tests with maternal and cord blood,¹⁹ but the substances measured are not of immunological importance. Until antigen-antibody relationships in this disease are better understood, it is wisest to act upon the assumption that the newborn infant will be susceptible to it, even though the reason for this cannot be stated.

Before leaving the subject of passive protection against infectious disease, the role of colostrum as a vehicle for antibodies deserves examination.²⁰ There is no doubt that this mechanism is one of extreme importance to newborn animals of certain species, as was shown by Theobald Smith's classical demonstration of the immunity against colon bacillus septicemia acquired by newborn calves with their first feedings. Most of the biological evidence indicates a rough relationship between the protective importance of colostrum and the complexity of the placental barrier.^{21,22} Thus in those animals, such as cattle and pigs, which have a placental structure interposing five tissue layers between the maternal and fetal circulations, the titer of various antibodies in the colostrum is high. Conversely, in species with hemo-chorial placentae which interpose only one tissue layer, the evidence for excretion and ingestion of colostrum antibodies is somewhat meager, while that for transplacental antibody passage is comparatively great. Species of this type include man, as well as the guinea pig, the rat, and other rodents.

Direct proof that human colostrum is of secondary significance as a source of protection to the infant has been more convincing than is this somewhat indirect reasoning based upon placental morphology. It has been shown, for example, that the colostrum of a mother contains relatively less diphtheria antitoxin than does her serum. Moreover, no increase in the titer of this antibody has been observable in the sera of infants ingesting colostrum, even of some antitoxic potency.^{9,23} On the other hand, evidence that agglutinins for the colon bacillus, as well as for other enteric organisms, are present in greater strength in colostrum and the later milk than in the infant's serum at birth, has been obtained by Toomey.²⁴ In fact, the cord sera of such infants possessed almost no agglutinating activity, but the agglutinin titer increased in samples of blood taken on succeeding days, which suggests that the in-

fants must have been acquiring antibody with their mothers' colostrum and milk. Indeed, the colostral level of agglutinins was observed to increase in parallel with that in the infants' sera, so that protection not available transplacentally appeared to be supplied by ingestion. It is worth noting that even minor concentrations of antibody absorbable from colostrum and milk might be serviceable to the infant because of the repeated opportunity for their ingestion.

Excretion of antibodies by the mammary glands has been demonstrated in connection with other roles played by these substances. Small amounts of skin-sensitizing antibodies, such as those specific for pollen and dust antigens, have been demonstrated occasionally in the colostrum of women with hay fever and asthma, although the colostral antibodies were much weaker than the seral.¹⁸ Of perhaps more clinical significance has been the recent demonstration by Witebsky and his colleagues,²⁵ of Rh antibody in the milk of a woman a week after she had given birth to an infant with erythroblastosis. The general subjects of allergic processes and hemagglutinin inter-relationships will be further considered below. The relative significance of transplacental and colostral antibodies in man may be summarized by stating that while the former are responsible for the majority of protective influences which the mother's body exercises over that of her baby, the latter cannot be completely minimized.

It was mentioned at the beginning of this chapter that beyond the factors assignable to ante-natal environment and post-natal nurture, there may be fundamental immunological differences between newborn infants and older subjects. Differences of this sort are of importance not only with regard to the unassisted defensive powers of the infant against infection, but also as they may affect the selection of satisfactory times for immunization procedures. Unfortunately, arguments concerning such immunological peculiarities, while supported by some observations and several impressions, are difficult to prove because of other processes simultaneously at work. A supposed "serological maturation," as Hirszfeld has called the concept of heightened antibody response with increasing age,²⁶ must be demonstrated during a period of life marked by increasing opportunities for the sub-clinical invasion of the body by small doses of infectious agents. Augmentation of "natural" antibodies by small increments thus acquired may furnish a satisfactory explanation for such well-known phenomena as the gradual increase in diphtheria immunity during childhood, without the postulation of any improved tissue efficiency in antibody manufac-

ture. These difficulties of interpretation are interestingly discussed in Topley and Wilson's textbook.²⁷

Animal experiments have yielded suggestive evidence that immature and mature organisms do differ, although observations have usually been made upon subjects a little beyond the immediately post-natal period. Baumgartner²⁸ has shown that young rabbits produce antibodies against *B. enteritidis* which are quantitatively and qualitatively inferior in agglutinating power to those produced under identical circumstances by older rabbits. Similar evidences of sub-optimal antibody response to typhoid bacilli as well as to foreign proteins and to heterologous red blood cells have been observed by Freund.²⁹ With regard to human subjects, it is said that young infants inoculated with typhoid bacilli do not always produce agglutinins,³⁰ though, on the other hand, active antibody protection against this antigen is mentioned above as having been observed in infants prenatally and transplacentally brought in contact with it. Children vaccinated against pertussis after the first six months of life apparently develop more adequate resistance than do infants similarly inoculated before the third month.³¹ The general impression also is that newborn infants vaccinated against smallpox do not attain so definite or so prolonged an immunity as that resulting from vaccination at 6 months or a year.³² However, Donnally³³ noted little difference except that infants vaccinated during the neonatal period manifested a somewhat smaller local reaction than did older subjects.

Certain tissues of the newborn infant are, if not immunologically immature, at least temporarily altered in reactivity. This is shown by the observation³⁴ that Schick tests performed during the neonatal period may frequently be negative although no antitoxin is present, as in infants born to mothers without diphtheria immunity. Various reasons might be advanced to explain this. It is possible but unlikely that the skin may be temporarily inferior in reactive capacity, as will be discussed in a later paragraph. On the other hand, the newborn may require less antitoxin than the adult for the prevention of a positive Schick reaction. In support of the latter possibility is the observation of Wadsworth and Hoppe³⁵ that cultures of embryonic tissue possess a neutralizing or destructive power against diphtheria antitoxin. It is not impossible that some such "tissue immunity" extends to other fundamentally significant defensive processes.

A limiting factor of importance in the production of antibodies is the availability of globulin, or of globulin-forming amino acids, to the organism. Cannon³⁶ has summarized the subject so well that

certain of his sentences should be quoted: "Antibodies are no longer to be regarded as mysterious 'forces' recognized mainly by what they do; they are, rather, molecules of globulin which, in the course of their synthesis, have been specifically modified by antigens. . . . These facts suggest that the synthesis of antibody globulin is but a part of the more basic process of the synthesis of normal globulin and that the solution of the problem of antibody production must be searched for at its source, that is, at the place of synthesis of globulin."

As has been stated earlier (Chapter IX), the moderate hypoproteinemia of the newborn infant is largely traceable to a failure of synthesis of serum globulin. The degree of this deficiency can be seen from these measurements³⁷ of globulin (in grams per 100 cc. of serum) at various ages:

Premature infants	1.01
Full-term newborn infants	1.34
Older infants (2-11 months)	1.38
Normal children	2.4

Since the globulin content of serum is in large measure correlated with antibody-production, it is evident that this process must in some way be curtailed not only during newborn life but for some time thereafter.

It has been thought that the neonatal globulin deficiency was to be completely explained by a differential permeability of the placenta which allows the free passage of *pseudoglobulins* but holds back the more significant *euglobulins*.^{38,39} In keeping with this, a progressive augmentation of euglobulins (as well as other globulins) has been shown to occur in the blood of calves coincidentally with their opportunities for suckling their mothers.^{40,41} But the persistence of reduced serum globulins, and probably, of cellular globulins as well, in human infants would indicate a rather prolonged inadequacy of globulin formation as more likely than a mere rejection of euglobulin by the placenta. The shortcoming of infants in this regard might therefore arise from immaturity of the cells responsible for globulin manufacture, or even from dietary deficiencies. It is also possible that the etiological relationship may be reversed, and that the diminished globulin may be caused by the lack of experience with antigens which call forth its production. The subject deserves investigation, which should include measurements of antibody globulin throughout infancy. The underlying explanation of Hirszfeld's "serological maturity" might be discovered in the cellular synthesis of proteins.⁴²

In summary, it may be said that inherent differences in resistance to infection do appear in the newborn as compared with the adult. So far as immediate response to infection is concerned, the difference may be one favorable to young tissues. As time passes and it becomes necessary for the infant to manufacture antibodies for replacement of those passively acquired, whatever advantages may accrue from a hypothetical "tissue immunity" are overshadowed by an inferiority in antibody manufacture as compared with the ability of the adult in this regard. There would seem to be sufficient reasons for postponing procedures of active immunization until six months or so after birth, but not much longer.

A basic argument for "serological immaturity" is drawn from studies of the agglutinogens and agglutinins whose pattern determines the *blood groups*. The subject is of sufficient clinical importance to be discussed as a whole, with the immunologically significant points indicated in passing.

The four major groupings of human blood are "dependent upon the presence or absence of two agglutinogens A and B in the red blood corpuscles and two agglutinins α (or anti-A) and β (or anti-B) in the serum."⁴³ The agglutinins (more properly called isoagglutinins or hemagglutinins) represent antibodies similar to antitoxins or bacterial agglutinins, with the important reservation that these particular antibodies appear in the serum as a natural property and without the necessity of stimuli from the introduction of cells carrying the specific isoagglutinogens.

The isoagglutinogens and isoagglutinins are first demonstrable at different periods of development, though the difference is probably one of relative titer as well as of simple presence or absence. Isoagglutinogens have been found in the red blood cells of the embryo as early as the 37th day of gestational life.⁴⁴ Although the titer increases through fetal and extra-uterine life, the essential arrangement determining the blood group seems never to alter,^{45,46} so that probably no infant is born, prematurely or otherwise, without the establishment of its permanent isoagglutinin pattern, and its blood group being already demonstrable.⁴⁷ Moreover, the other and less frequently determined isoagglutinogens identified as M, N, and Rh, have been found in embryos of 7 cm. in length,⁴⁶ at which time they appear to be as unalterably established for the individual as are the A and B factors.

On the other hand, the isoagglutinins of the organism put in a later appearance.⁴³ The serum of the newborn infant may indeed contain easily demonstrable isoagglutinins in about 50% of cases, but these are of maternal origin and have been passively transferred

to the infant across the placenta *in utero*. As a result it is obvious that the infant's serum contains no significant isoagglutinins against the mother's cells.^{43,48} The maternal isoagglutinins disappear from the infant within the first ten to fourteen days following birth, after which the formation of the infant's own isoagglutinins becomes increasingly apparent. Though their origin is said to occur in the antenatal period⁴³ the concentration of these agglutinins does not usually reach clinical importance until some weeks or months after birth.⁴⁹ Like the agglutinogens, the peak of their activity is reached with maturity. It is in this rather sluggish development of isoagglutinins that a major argument has been found for the comparative inadequacy of newborn subjects to manufacture antibodies in general.

This is not the place to discuss the genetic aspects of the isoagglutinins and agglutinogens,⁴³ but something should be said of their obvious importance in regard to transfusion and to the question of hetero-antibody relationships between maternal and fetal blood. In transfusing blood to newborn patients it has often been assumed that the infant "has not yet developed a blood group," that attempts to determine such a group, or to cross-match the recipient's and the donor's blood are therefore unnecessary, and that any donor may be used. Actually this is not true for several reasons. The usual transfusion of 10 cc. (or even more) blood per pound of the infant's weight introduces an amount which is relatively much greater than that given to older recipients. A 500 cc. transfusion dilutes the blood of an adult by about one-fifteenth; a 70 cc. transfusion dilutes the blood of a newborn infant by about one-fifth. As a result, the possibility that the donor's antibodies may affect the recipient's cells is a very real one. Moreover, the sera of some infants do have agglutinins passively acquired from the mother. Some of these may be of such a type as would be compatible with maternal blood, were that used in an emergency for an un-matched transfusion, but others would render transfusion from the mother distinctly unwise, as will be discussed below. Finally, as Wiener has pointed out⁴³ infants are often transfused more than once over a period during which their own isoagglutinins are increasing; thus the repeated use of blood from the same donor without repeated cross-matching may be no guarantee of safety in subsequent transfusions even though the first was without accident.

An important advance in knowledge of those maternal-fetal relationships which have a definite bearing upon the immunological possibilities of neonatal life has been the inference from Levine's work⁵⁰ that the red blood cells of the fetus can escape across the

placenta to the mother's body so that the antigens attached to these cells, if foreign to the maternal pattern, may induce specific responses in her serum. The placenta, as in the case of so many antibodies discussed above, is sufficiently permeable to allow these to pass back into the fetus with significant results. In the disease called erythroblastosis fetalis, which apparently arises in this way, hemolysins induced in the mother's serum bring about so severe a destruction of fetal erythrocytes as to result in that overproduction of immature cells which gives the condition its name. The Rh substance mentioned above is the best known (at present) of the specific agglutinogens of the fetus responsible for this train of events. Others are under investigation. The Rh agglutinin is absent from the blood of about 15% of Caucasian individuals, so that the basically required situation of Rh+ father, Rh- mother, and Rh+ fetus is brought about with some frequency. Fortunately, the necessary migration of cells from infant to mother, and of serum in the reverse direction does not occur in every such circumstance. When it does occur and when the infant manifests the resultant hemolytic anemia, there arises an urgent need for transfusion and for special caution in selection of the proper donor. Obviously the use of maternal blood will only increase the exposure of the infant's cells to undesired anti-Rh activity, whereas the father's blood introduces cells which will be attacked by such antibody as remains in the infant from its mother's serum. The donor of choice must be an Rh- individual who has not had recent stimulus (through pregnancy or the receipt of a transfusion) for production of anti-Rh substances. The observation of Witebsky²⁵ that the antibody also is excreted in the colostrum or milk of women after birth of an erythroblastotic infant has been mentioned above. The condition is thus one in which either trans-placental or colostral antibodies are harmful rather than useful to the infant.

Not only may the presence of Rh+ cells in the fetus of an Rh- mother induce potential or actual complications by means of placental passage. It has also been shown⁶¹ that a mother of blood group O may develop a higher titer of anti-A agglutinin if she is carrying a fetus with the A agglutinin than if the fetus were group B or O. Such a development would of course render her a most unsuitable donor for transfusion of blood to her infant, and thus offers one more reason for careful cross-matching of blood in transfusions to the newly born patient.

As with the strictly infectious aspects of immunology, there are various *allergic aspects* in which the newborn infant may have its individuality. Again, investigation has been concerned with the

reception of antigens and antibodies by the fetus *in utero* and, through various routes, by the newborn infant. Study has also been devoted to the question of fundamental peculiarities of reactive capacity which might characterize fetal or newborn tissues in general, without regard to particular opportunities for acquiring hypersensitivity.

The latter question may be first discussed, as its answer is of primary importance to the former one. The skin of the newborn infant, if locally sensitized with serum from an allergic adult, has been shown to be quite capable of whealing when the specific antigen was injected thereafter. Cutaneous sensitivity to materials which produce wheals when injected into the skin of non-atopic or atopic adults seems to be very nearly as marked in the skin of infants from 5 to 48 hours of age. Sulzberger and Baehr,⁵² who recently demonstrated this with solutions of histamine and of codeine, therefore believe that cutaneous reactivity is not impaired by neonatal conditions and that a neonatal absence of response to such commonly effective intradermal test substances as house dust can only mean that such materials possess no "primarily irritating" or "primary urticariogenic" properties.

Actually a large and unselected series of infants were shown by Vollmer and others⁵³ to be entirely unresponsive to intradermal injections of milk, egg, and other protein substances at 12 hours of age, even though a positive family history of allergy was obtainable in the usual percentage of the group, and although several had reactions to the same substances on retesting 2 to 24 months later. It would appear that the lack of response displayed by such infants immediately after birth can scarcely be assignable to inadequacy of cutaneous reactivity. Whether some process more fundamental than cutaneous reactivity is at fault has not yet been discovered. Although newborn infants rarely if ever display the skin sensitive phenomena of allergy, hypersensitivity not infrequently appears within a few weeks after birth and sometimes to substances with which no direct contact has been known to occur.

The question then arises as to the mechanisms by which newborn infants acquire such hypersensitivity. Antigen might reach the infant either across the placenta or in the food, whereas specific maternal antibody might be transferred in either of these manners also. Ratner and his colleagues have reviewed the literature on placental passage of those protein molecules usually acting as antigens, and have added proof of their own that fetal animals may thus be sensitized.^{23,54} There is clinical evidence to support the view that similar passage of allergically important antigens occurs in

some human subjects.⁵⁴ That the neonatal intestinal wall may be particularly vulnerable to the passage of undigested protein is suggested by the immaturity of digestive action and the structural delicacy characterizing this stage of development. Until recently the absorption of pure proteins has been less investigated in adult human and animal subjects than in neonatal ones. So frequently was evidence obtained for a supposedly excessive intestinal permeability during the newborn period that one observer⁵⁵ concluded that the intestinal wall at birth is naturally lacking in the intact layer of mucus which normally covers the epithelium. Such an anatomical peculiarity was later and convincingly denied by others,⁵⁶ but the idea persists that protein penetration through the intestinal wall must be possible only at very early ages,⁵⁷ or during gastrointestinal disturbances in older subjects.⁵⁸ The direction of more recent studies has been to show that the phenomenon, though perhaps slightly more easily brought about in newborn babies, can also be demonstrated in quite healthy older infants⁵⁹ and in adults,⁶⁰ so that there seem to be very few grounds for assuming an entirely unique status of the neonatal digestive tract in the absorption of unsplit protein molecules.

In any case there is little doubt that fetuses and newborn infants are, like older people, constitutionally variable in their response to foreign proteins by whatever route these enter the blood, and that such an event may produce marked hypersensitivity in one subject but none in another. Given a constitution favoring allergic responsiveness, the antigen which sets the train in motion may probably be received by the fetus transplacentally or by the infant, child, or adult, through the intestinal wall. Why a promptly developing neonatal sensitivity is rarely if ever demonstrable remains unexplained.

Transplacental absorption of so-called skin-sensitizing *antibodies* has been an easier problem for investigation. A review of published studies, most of them with negative results, may be found in Sherman, Hampton, and Cooke's recent paper.¹⁸ These authors found that whereas the sera of pregnant women with asthma and hay fever carried antibodies of high titer (to pollens, dusts, etc.) as demonstrated by passive transfer, the cord sera of their offspring were routinely negative for any evidence of placental passage obtainable by similar tests. Moreover, direct skin and passive transfer testing of the same infants 3 to 6 months later did not demonstrate any antibodies similar to those of their mothers. This argues against a masking of neonatal sensitivity by transitory peculiarities of the newborn period. The authors also proved that other antibodies

which are developed in hay fever patients under specific therapy, and designated as "blocking" antibodies, could pass to the fetuses of these mothers. Such antibodies are heat stable, as compared to the thermolabile skin-sensitizing ones, and thus offer further examples of the fact that placental transmission is in some way a selective process.

One piece of evidence available from experiments upon the monkey indicates that placental transfer of such antibodies as often exist in atopic human patients is possible in that animal, and therefore that its occurrence in man is not necessarily out of the question.⁶¹ It may be that, as Wiener and Silverman⁶² have attempted to show, there is a quantitative relationship or ratio between the amount of maternal antibody and the amount which will cross the placenta. According to these authors such a ratio lies somewhere between 8 to 1 and 16 to 1. In other words, for one arbitrary unit of skin-sensitizing antibody to appear in the fetal blood, from 8 to 16 units must be present in the maternal. Were this substantiated it would imply the possibility that negative experiments would result in the case of a maternal antibody level insufficient to surmount the placental threshold. With present evidence this seems an unlikely explanation of the routine failure of skin-sensitizing antibodies to be found in the fetus. That the placenta acts protectively by absorbing certain deleterious antibodies, and thus not allowing them to go further, has been suggested by Coca,⁶³ but extracts from the placenta have not been shown to possess any concentration of skin-sensitizing antibodies,¹⁸ so that this hypothesis remains decidedly unproven.

CLINICAL SUMMARY

Newborn infants are protected by a **passive immunity** against a number of infectious diseases, provided that the mother has had opportunity to become resistant to them. Among the commoner *antibodies* passing the placenta are diphtheria and tetanus antitoxins, and immune bodies opposing the viruses of measles, chicken pox, smallpox, mumps, poliomyelitis and the ordinary upper respiratory infections. Although such protection is relative, it probably lasts for about six months or longer. A shorter-lived resistance is also demonstrable against the pneumococcus and influenza bacillus, against scarlet fever and certain other streptococcal processes, against staphylococcal toxins, and against at least one of the antigenic fractions of the typhoid bacillus. Protection against pertussis is usually negligible, although it can be increased by active immunization of the mother during pregnancy. Of the routes by

which maternal antibodies reach the fetus and infant, prenatal passage across the placenta is probably more important than post-natal ingestion of colostrum antibody, though the latter may be of real significance as a source of relative immunity against enteric infections.

Since maternal antibodies are necessary for any passive acquisition of immunity by the infant, and since all mothers do not have antibodies against the infections just mentioned, infants may be born in the active stage of several common contagious diseases. Thus viral (as well as other) *antigens* may cross the placenta. Apparently this seldom or never occurs in poliomyelitis because the virus is not free in the mother's blood.

While there may be a certain non-specific "tissue immunity" inherent in rapidly proliferating cells such as those of the fetus and newborn, the specific and **active immunity** responses to antigenic stimuli are less efficient in the neonatal period than in later infancy. Therefore, the usual prophylactic inoculations are best deferred until the second six months of life unless there is some special reason for beginning them earlier. Neonatal inadequacy of antibody production may well be related to the characteristically low concentration of serum (and cellular) globulins in young infants.

The isoagglutinogens determining the **blood groups** are present in the red blood cells long before birth, though they increase in strength during intra-uterine and extra-uterine life. The isoagglutinins also follow a rising curve, but are of relatively less importance during the newborn period than are the agglutinogens. Maternal isoagglutinins often appear by transplacental passage in the infant's blood. On the other hand, agglutinogens attached to fetal cells seem able to cross to the maternal side of the placenta and evoke responses sometimes capable of producing dangerous blood destruction in the fetus and infant (erythroblastosis), or, under other circumstances, rendering the mother's blood decidedly unsuitable for transfusion to her baby. For this and several other reasons discussed more fully above, only blood which has been proven compatible by cross-matching should be used for the transfusion of newborn patients.

Problems of **allergy** are related to those of immunity but present special difficulties of interpretation. It seems probable that constitutionally susceptible infants may be sensitized to allergens received by trans-placental passage or by early post-natal ingestion. The infant's skin has been shown to be similar to the adult's in its capacity for wheal formation under experimental circumstances. Nevertheless, no reports have been found of significant skin sensi-

tivity to allergically important protein substances during the first few weeks of life, infants who show such responses by skin tests at several months of age having been negative to the same tests shortly after birth. Many attempts have been made to discover whether skin-sensitizing antibodies from the blood of allergic mothers might pass to the fetus and thus induce passive hypersensitivity in the infant, but all have given essentially negative results. Why the infant should be so fortunate as to be born with an assortment of passively accepted antibodies against infection but to escape a simultaneously acquired burden of undesirable antibodies of allergic significance has not been determined. Nor do we know why the transplacental passage of allergically important antigens so rarely results in clinical manifestations of immediate post-natal hypersensitivity and can seldom if ever be demonstrated by skin tests at this time. Since constitutional differences play an undoubted role, caution in the early administration of certain dietary proteins to infants of allergic parents is obviously warranted. This might be urged with greater emphasis if the degree of danger were known.

BIBLIOGRAPHY

1. SSACHAROFF, G. P.: Infektionskrankheiten und Altersdisposition, *Ergebn. d. allg. Path. u. path. Anat.* 22: 201, 1928.
2. MCKHANN, C. F., and KAPNICK, I.: Immunity and susceptibility to disease in early infancy, *J. Pediat.* 13: 907, 1938.
3. BAUMGARTNER, L.: Relationship of age to immunological reactions, *Yale J. Biol. & Med.* 6: 403, 1934.
4. SHUMAN, H. H.: Varicella in newborn, *Am. J. Dis. Child.* 59: 564, 1939.
5. HARMON, P. H., and HOYNE, A.: Poliomyelitis and pregnancy, with special reference to failure of fetal infection, *J. A. M. A.* 123: 185, 1943.
6. LIEBLING, J., YOUMANS, G. P., and SCHMITZ, H. E.: Occurrence of diphtheria antitoxin in human pregnant mother, newborn infant, and placenta, *Am. J. Obst. & Gynec.* 41: 641, 1941.
7. COHEN, P., and SCADRON, S. J.: Placental transmission of protective antibodies against whooping cough by inoculation of the pregnant mother, *J.A.M.A.*, 121: 656, 1943.
8. NEEDHAM, J.: *Chemical Embryology*, Volume 3, New York, The Macmillan Company, 1931.
9. KUTTNER, A., and RATNER, B.: The importance of colostrum to the newborn infant, *Am. J. Dis. Child.* 25: 413, 1923.
10. NEILL, J. M., GASPARI, E. L., RICHARDSON, L. V., and SUGG, J. Y.: Diphtheria antibodies transmitted from mother to child, *J. Immunol.* 22: 117, 1932.
11. TENBROECK, C., and BAUER, J. H.: The transmission of tetanus antitoxin through the placenta, *Proc. Soc. Exper. Biol. & Med.* 20: 399, 1922-23.
12. SUTLIFF, W. D., and FINLAND, M.: Antipneumococcic immunity reactions in individuals of different ages, *J. Exper. Med.* 55: 837, 1932.

13. FOTHERGILL, L. D., and WRIGHT, J.: Influenzal meningitis, *J. Immunol.* 24: 273, 1933.
14. TOOMEY, J. A., and AUGUST, M. H.: Studies in scarlet fever; blanching with placental serum, *Am. J. Dis. Child.* 38: 953, 1929.
15. TODD, E. W.: Antihæmolytic titres in hæmolytic streptococcal infections and their significance in rheumatic fever, *Brit. J. Exper. Path.* 13: 248, 1932.
16. LIGHTY, J. A., JR., and ANDERSON, G. K.: Streptococcal anti-fibrinolysin in newborn infants; true and false tests, *Am. J. Dis. Child.* 65: 60, 1943.
17. BRYCE, L. M., and BURNET, F. M.: Natural immunity to staphylococcal toxin, *J. Path. & Bact.* 35: 183, 1932.
18. SHERMAN, W. B., HAMPTON, S. F., and COOKE, R. A.: Placental transmission of antibodies in skin sensitive type of human allergy, *J. Exper. Med.* 72: 611, 1940.
19. WEICHSSEL, M., and DOUGLAS, H. S.: Complement fixation tests in pertussis, *J. Clin. Investigation* 16: 15, 1937.
20. FAMULENER, L.: On the transmission of immunity from mother to offspring, a study upon serum hemolysins in goats, *J. Infect. Dis.* 10: 332, 1912.
21. MASON, J. H., DALLING, T., and GORDON, W. S.: Transmission of maternal immunity, *J. Path. & Bact.* 33: 783, 1930.
22. (a) SCHNEIDER, L., and SZATHMÁRY, J.: Ueber die Immunität der Neugeborenen Säugtiere, *Ztschr. f. Immunitätsforsch. u. Exper. Therap.* 94: 458, 1938.
(b) SCHNEIDER, L., and SZATHMÁRY, J.: Ueber die Immunität der Neugeborenen Meer-schweinchen, *Ibid.* 98: 24, 1940.
23. RATNER, B., JACKSON, H. C., and GRUEHL, H. L.: Transmission of protein hypersensitiveness from mother to offspring... (5 papers), *J. Immunol.* 14: 249, 1927.
24. TOOMEY, J. A.: Agglutinins in mother's blood, baby's blood, mother's milk, and placental blood, *Am. J. Dis. Child.* 47: 521, 1934.
25. WITEBSKY, E., ANDERSON, G. W., and HEIDE, A.: Demonstration of Rh antibody in breast milk, *Proc. Soc. Exper. Biol. & Med.* 49: 179, 1942.
26. HIRSZFELD, H., HIRSZFELD, L., and BROKMAN, H.: On the susceptibility to diphtheria (Schick test positive) with reference to the inheritance of blood groups, *J. Immunol.* 9: 571, 1924.
27. TOPLEY, W. W. C., and WILSON, G. S.: *The Principles of Bacteriology and Immunity*, 2nd Ed., Chapter 46, Baltimore, Wm. Wood & Co., 1936.
28. BAUMGARTNER, L.: Age and antibody production, *J. Immunol.* 27: 407, 1934.
29. FREUND, J.: Influence of age upon antibody formation, *J. Immunol.* 18: 315, 1930.
30. FRANKENSTEIN, C.: Zur Frage der aktiven Immunisierung im Säuglingsalter, *Zeitschr. f. Kinderh.* 25: 12, 1920.
31. SAUER, L. W.: Age factor in active immunization against whooping cough, *Am. J. Path.* 17: 719, 1941.
32. TOP, F. H., and others: *Handbook of Communicable Diseases*, St. Louis, C. V. Mosby, 1941.
33. DONNALLY, H. H., and NICHOLSON, M. N.: A study of vaccination in five hundred new-born infants, *J. A. M. A.* 103: 1269, 1934.
34. COOKE, J. V., and SHARMA, B. M.: Schick test in newly born, *Am. J. Dis. Child.* 44: 40, 1932.

35. WADSWORTH, A. B., and HOPPE, E. N.: The neutralization or destruction of diphtheria toxin by tissue, *J. Exper. Med.* 53: 821, 1931.
36. CANNON, P. R.: Antibodies and the protein-reserves, *J. Immunol.* 44: 107, 1942.
37. RAPOPORT, M., RUBIN, M. I., and CHAFFEE, D.: Fractionation of serum and plasma proteins by salt precipitation in infants and children; changes with maturity and age; changes in glomerulonephritis; changes in nephrosis, *J. Clin. Investigation* 22: 487, 1943.
38. LEWIS, J. H., and WELLS, H. G.: The function of the colostrum, *J.A.M.A.* 78: 863, 1922.
39. BOYD, G. L.: The value of colostrum to the newborn, *Canad. M.A.J.* 12: 724, 1922.
40. HOWE, P. E.: An effect of the ingestion of colostrum upon the composition of the blood of newborn calves, *J. Biol. Chem.* 49: 115, 1921.
41. ORCUTT, M. L., and HOWE, P. E.: The relation between the accumulation of globulins and the appearance of agglutinins in the blood of new-born calves, *J. Exper. Med.* 35: 291, 1922.
42. CANNON, P. R., CHASE, W. E., and WISSLER, R. W.: Relationship of protein-reserves to antibody-production; effects of low protein diet and of plasmapheresis upon formation of agglutinins, *J. Immunol.* 47: 133, 1943.
43. WIENER, A. S.: *Blood Groups and Blood Transfusion* (Ed. 3). Springfield, Charles C Thomas and Company, 1943.
44. KEMP, T.: Über den Empfindlichkeitsgrad der Blutkörperchen gegenüber Isohämagglutininen im Fötalleben und im Kindesalter, *Acta Path. et. Micr. Anat. Scand.* 7: 146, 1930.
45. HYMAN-PARKER, H. S.: Development of agglutinogens M and N in newborn infants with notes on agglutinogens A and B, *J. Immunol.* 43: 1, 1942.
46. BORNSTEIN, S., and ISRAEL, M.: Agglutinogens in fetal erythrocytes, *Proc. Soc. Exper. Biol. & Med.* 49: 718, 1942.
47. SMITH, C. H.: Iso-agglutinins in new-born, with special reference to their placental transmission, *Am. J. Dis. Child.* 36: 54, 1928.
48. POLAYES, S. H., LEDERER, M., and WIENER, A. S.: Studies in isohemagglutination; Landsteiner blood groups in mothers and infants, *J. Immunol.* 17: 545, 1929.
49. THOMSEN, O., and KETTEL, K.: Die Stärke der menschlichen Isoagglutinine und entsprechenden Blutkörperchenrezeptoren in verschiedenen Lebensaltern, *Zeitschr. f. Immunitätsf.* 63: 67, 1929.
50. (a) LEVINE, P., KATZIN, E. M., BURNHAM, L.: Iso-immunization in pregnancy; its possible bearing on etiology of erythroblastosis foetalis, *J. A. M. A.* 116: 825, 1941.
(b) LEVINE, P.: The pathogenesis of erythroblastosis foetalis, *J. Pediat.* 23: 656, 1943.
51. JONSSON, B.: Zur Frage der heterospezifischen Schwangerschaft, *Acta path. et Microbiol. Scandinav.* 13: 424, 1936.
52. SULZBERGER, M. B., and BAEHR, R. L.: Whealing capacity of skin of newborn or young infant; report of experiments, *Arch. Dermat. & Syph.* 41: 1029, 1940.
53. VOLLMER, E. S., WILMER, H. B., and MILLER, M. M.: Skin-reactivity in newborn, *Internat. Clin.* 4: 63, 1940.
54. RATNER, B.: Allergy in childhood; I. The modes of its acquisition, *J. Pediat.* 12: 730, 1929.

55. DISSE: Untersuchungen über die Durchgängigkeit der jugendlichen Magen-Darmwand für Tuberkelbacillen, Berl. Klin. Wchnschr. 40: 4, 1903.
56. v. D. LEYEN, E.: Über die Schleimzone des menschlichen Magen- und Darmepithels vor und nach der Geburt, Virchow's Arch. f. path. Anat. 180: 99, 1905.
57. GANGHOFNER, and LANGER, J.: Resorption genuiner Eiweisskörper in Magendarmkanal neugeborener Tiere und Säuglinge, München. med. Wchnschr. 51: 1497, 1904.
58. SCHLOSS, O. M., and WORTHEN, T. W.: The permeability of the gastroenteric tract of infants to undigested protein, Am. J. Dis. Child. 11: 342, 1916.
59. LIPPARD, V. W., SCHLOSS, O. M., and JOHNSON, P. A.: Immune reactions induced in infants by intestinal absorption of incompletely digested cow's milk protein, Am. J. Dis. Child. 51: 562, 1936.
60. RATNER, B., and GRUEHL, H. L.: Passage of native proteins through the gastrointestinal wall, J. Clin. Investigation 13: 517, 1934.
61. COHEN, M. B., COHEN, S., and HAWVER, K.: Transmission of reagin through placenta, Proc. Soc. Exper. Biol. & Med. 41: 477, 1939.
62. WIENER, A. S., and SILVERMAN, I. J.: Permeability of the human placenta to antibodies; quantitative study, J. Exper. Med. 71: 21, 1940.
63. COCA, ARTHUR F.: Asthma and Hay Fever in Theory and Practice; Part 1. Hypersensitiveness, Anaphylaxis, Allergy. Springfield, Charles C Thomas and Company, 1931.

INDEX

A

- Acid-base equilibrium, 252, 256
 - in premature, 255
 - neonatal, 253
 - total, base*
- Acidosis, and gastric acidity, 177
 - in prematures, 253, 256
 - neonatal, 254
 - treatment, 257
- Adrenalin, 268
- Adrenals, cortex, fetal, 266
 - cortical hormone, 266, 267
 - effect on newborn, 268
 - virilism, 267
- Adreno-genital syndrome, 267
- Agglutinins, 287. See also Antibodies; Antigens; Blood groups; Immunity
 - for colon bacillus in colostrum, 283
- Agglutinogens and agglutinins, 287-289, 293
 - Rh, 287, 289
- Air in gastrointestinal tract, 48, 169, 173
 - Albumin, serum,*
- Albuminuria, 250, 256
- Allergy, and immunity, 289-292
 - tests in newborn, 290, 293
- Amino acids, 187
 - in, blood from cord and from mother, 189
 - fetus and mother, 189
 - urine, 188, 191
 - metabolism, 187
 - incomplete, corrected by giving ascorbic acid to premature infants, 235
 - nitrogen in blood, 191
- Amniotic fluid in lungs, 39, 40
 - inhalation, 39, 40
 - renal component, 243
 - swallowed by fetus, 167
- Amylase in fetus, 174
 - pancreatic, at birth, 179
- Androgens; androgenic activity in fetal
 - adrenal cortex, 267
 - and sex of infant, 265
 - in placenta, 266
- Anemia, physiological, 230, 238
- Anesthesia, effect on fetal respiration, 11
 - effect on neonatal respiration, 34, 58
- Anoxemia. See Blood, oxygen; Oxygen deficiency
- Anoxia. See Oxygen, deficiency

* See inside back cover.

- Antibodies, 280-291
 - antitoxic, 281, 282
 - antiviral, 281, 282
 - bactericidal, 282
 - excretion by mammary glands, 284
 - fetal, 280-281
 - in colostrum, 283
 - production and serum globulin, 286
 - effect of age, 285
 - transplacental absorption of skin-sensitizing antibodies, 291
- Antifibrinolysin, 282
- Antigens, placental transfer, 281, 282
- Antistreptolysin, 282
- Aortic and carotid chemo-receptors,
 - in neonatal respiration, 34, 57
- Apnea, 19
 - decrease in oxygenation of fetal blood
 - during induced apnea, 16
 - high oxygen environment in, 36, 58
 - induced, decrease in oxygenation of fetal blood during, 16
- Arteries, injection preparation showing
 - arterial system and relative sizes of its vessels, in stillborn, 82
- Ascorbic acid. See Vitamin C
- Asphyxia, carbon dioxide tension in
 - newborn, 22
 - coramin in, 35
 - high oxygen environment, 36, 58
 - in newborn, 33
 - causes, 33
 - in low levels of oxygenation, 19
 - influence of carotid and aortic bodies, 35, 57
 - lobeline injection, 35
 - nikethamide in, 35
 - pulsation in cord vessels in, 72
- Asthma, antibodies in colostrum, 284

B

- Bacteria in alimentary tract, and in feces, 180
 - neonatal, type of organisms, 181
 - meconium, type of organism, 181
- traced to maternal vagina, skin of breast, and other objects in contact with baby's face, 181
- types found in gastrointestinal tract, 181
- Bactericidal antibodies, 282
- Beriberi and vitamin B complex, 236
- Bicarbonate ion, 252,*
- Bile, pigment in meconium, 130

- Bilirubin*. See also Bile, pigments in, blood. See Blood, bilirubin; Icterus neonatorum
feces, and urine in newborn, 134
correlation with presence or degree of icterus, 132
meconium, 131
- Bleeding time, 118*
- Blood. See also Erythrocytes; Hemoglobin; Leukocytes
acid-base equilibrium. See Acid-base equilibrium
amino acids in. See Amino acids
bicarbonate ion concentration, 252,*
bilirubin. See also Icterus neonatorum and oxygen, 131
concentrations, distribution in cord and later serum of normal infants during neonatal period, 128
in umbilical cord serum of normal infants, 128
correlation between degree of increase in, and presence or absence of jaundice, 129
excessive at birth, 131
due to post-natal hemolysis, 132, 135
in prematures, 133
in cord blood, 129
jaundice due to excess, 129
normal amount, 129
relation between serum bilirubin concentrations and degree of jaundice, 128
Van den Bergh reaction, 130
calcium, 221-227, 237,*
and parathyroid secretion, 273
filterable or diffusible, 226
in maternal serum, at birth, 226
ionized, 226
measurements in prematures, 237
carbon dioxide,*
and oxygen of human fetus, 18-22
at and before birth, 21
dissociation curves, 23
effect on fetal respiration, 16
fetal, 18
tension, and asphyxia, 34
at birth, 22
in newborn, 22
carbonic anhydrase in fetal and neonatal blood, 28, 29
chlorides, 252,*
cholesterol, 212*
- * See inside back cover.
- Blood—*continued*
circulation. See also Heart
capillaries, 84, 85. See also Capillaries
clinical summary, 96
distribution of blood, 81-82
dynamics, 86-90
fetal, and its alterations at birth, 63-70, 96
and neonatal blood volume, 73
crossing or mixture of streams, 63, 65, 66, 96
oxygen saturation of blood leaving placenta, 64
pulmonary circuit, 66
summary, 96
placental circulation, percentage of blood in, 73
response to oxygenation of blood passing through, 71
through lungs, 96
time, 89-90
and pulse rate, 86, 90. See also Pulse, rate
work of fetal and neonatal heart, 76
coagulation, 116-120,*
bleeding time, 118*
clotting time at birth, variations in, 118
fibrinogen, 119
fetal, 120
in newborn, 122
maternal, 120
platelets from birth to 3 months, 117
prolonged, 118
prothrombin, 118,*
fluctuations in prematures, 119
time, 121
vitamin K, 117-121
count. See Blood, platelets; Erythrocytes; Leukocytes; Lymphocytes
creatinine and creatinine, neonatal, 195
electrolytes. See Electrolytes
estrogens. See Estrogens
fats, 207-213, 215,*
human fetal blood, 210
maternal, 211
neonatal, 211-213
newborn and adult, 213
percentage composition of total lipids, 213
fibrinogen, 119. See also Blood, coagulation
and sedimentation rate, 120
fetal, 120
in newborn, 122
maternal, 120

Blood—*continued*

- gases, fetal, 13-18. See also Blood, carbon dioxide; Blood, oxygen
- globulins. See Blood, proteins
- glucose. See Blood, sugar
- groups, 287-289, 293
- hemoglobin. See Hemoglobin
- hormones. See Estrogens; Hormones
- hydrogen ion concentration, 254, 256,*
- iodine, 270
- lipoids. See Blood, fats
- morphology, prenatal, 103
- neonatal, clinical summary, 120. See also various subheads under Blood
- nitrogenous substances in, 187-200
 - average concentrations of, 189
 - in neonatal blood, 194
- non-protein nitrogen, 187, 188, 194,*
 - components, 214
 - in fetus, 188
- oxygen. See also Blood, gases
 - and carbon dioxide, 14, 18-22
 - levels in human and animal fetal blood, 19
 - anoxemia and fetal respiration, 16
 - at birth, 35-39, 47
 - content of blood from carotid and umbilical arteries, 65
 - dissociation curves of goat fetus and mother, 25
 - human infants at birth, 26
- exchange through integument, 48-49
- from umbilical vein and arteries, 18
- in right and left ventricles in fetus, 65
- in umbilical vessels, 71, 72
- levels depressed by handling cord, 19
- maternal anoxemia reflected by anoxemia in fetus, 19
- oxygen in gastro-intestinal tract taken up by blood, 48
- post-natal adjustment of arterial blood, 37-39
- response of placental vessels to oxygenation of blood, 71
- role in closure of ductus arteriosus, 69
- phosphatase,*
 - at birth, 228
- phosphorus, 227-228, 237,*
- platelets at birth, 116-117, 121,*
- potassium, 252,*

* See inside back cover.

Blood—*continued*

- pressure,*
 - capillary, 86, 97
 - cuff size as factor, 93, 95, 97
 - diastolic, 95
 - effect of, clamping cord, 91
 - onset of respiration on, 91
 - fetal and neonatal, 91-95
 - in right and left ventricles in fetus, 92
 - in sheep, 91
 - premature infants, 91, 95
 - relation to weight at birth, 95
 - systolic, 93, 95
 - umbilical artery, 92, 97
- proteins, 197-200*
 - globulin content at various ages, and antibody production, 286
 - hypoproteinemia, 286
 - in premature infants, 198
 - relation between edema and plasma proteins, 200, 214
 - serum,*
 - albumin,*
 - globulin,*
- red cells. See Erythrocytes
- respiratory function. See Respiration and blood
- reticulocytes at birth, 109
- sedimentation, rate of erythrocytes, 120, 122,*
- sodium, 251,*
- sugar, 200-207,*
 - and insulin secretion, 271, 272
 - at birth, 201
 - in fetus, 201
 - premature infants, 203, 205
 - summary, 215
 - tolerance studies after ingestion of various sugars, 205
- transfusion, determining blood for, 288, 293
 - of adult blood during neonatal period, 29
- urea, 187,
 - nitrogen, 193, 194*
- uric acid, 188, 196, 197, 214,*
 - and renal infarcts, 197
- vessels, distribution in newborn, 81-86, 97
- vitamins. See Vitamins
- volume,*
 - at birth, 73, 74, 76, 96
 - fetal and neonatal, 73-77
 - in newborn and adults, 76
 - percentage in placental circulation at birth, 74, 96
 - white cells. See Leukocytes

- Body surface, and body weight at various ages, 142
 area in regulating heat loss, 141
 formulae for computing, 141
 respiration and, 54
 temperature. See Temperature
 weight. See Weight
- Bone and calcium metabolism, 221
 phosphatase activity in, 229
- Brain, oxygen consumption of various parts during growth, 36
- Breast, antibodies excreted by, 284
 changes at birth, 262, 274
 enlargement, 262
 secretion, 262
 in prematures, 262

C

- Calcium, 221-227*
 equilibrium, 223
 in, blood. See Blood, calcium
 human and cow's milk, 223
 increase, 222
 loss in feces, 223
 metabolism, 221
 retention, in premature infants, 224
 on diet of cow's and human milk, 224, 237
- Calories, requirements of, newborn period, 151, 162
 of premature infants, 152, 162
- Capillaries, 83-86. See also Blood vessels
 blood pressures in newborn, 86, 97
 changes in cyanosis, 85
 of premature, 85
 permeability for electrolytes and fluids, neonatal, 86, 97
 resistance, 83
 summary, 97
- Carbohydrate, assimilation and metabolism, 200-207, 214, 215
 source of fetal energy, 201
- Carbon dioxide in blood. See Blood
- Cardio-thoracic index, 79, 96
- Carotene, 233. See also Vitamin A
- Carotid and aortic chemo-receptors, role in onset of respiration, 34, 35, 57
- Chest. See Thorax
- Cheyne-Stokes breathing, 55, 56
- Chicken pox, antibodies in newborn, 281, 282, 292
- Chloride ion in blood, 252*
 retention on diet of cow's and human milk, 224
- Cholesterol metabolism, 212
- * See inside back cover.
- Circulatory system. See Blood, circulation
- Cog-wheel respiration, 55, 56
- Cold, common, neonatal resistance, 282, 292
- Colon, neonatal, 168, 172
 roentgenology, 168
- Colostrum and uric acid, excretion, 197
 antibodies in, 283, 284
 as source of vitamin A, 234
 protein and fat content, 191, 215
- Coramin in asphyxia, 35
- Corpus luteum hormones in newborn, 263
- Creatine, in blood and urine, neonatal, 195
 in urine, 188
- Creatinine, in blood and urine, neonatal, 195
 in urine, 188
 metabolism, 195, 196
- Cretinism; cretinoid characteristics in fetus, 269, 275
- Crying and metabolism, 143
- Cyanosis, capillary changes, 85

D

- Dehydration and increase in leukocytes
 in newborn, 116
 fever, chloride ion in, 252
 in newborn, 256
 causes, 249
- Diabetes in mother, and hyperinsulinism in newborn, 271, 272, 275
- Diaphragm, 49, 50
- Diet. See also Food; Nutrition
 caloric basis for feeding newborn, 162
 carbohydrate in, 206
 effect on mineral retention, 224
 fats in, 207
 requirements during newborn period, 151, 162
- Digestive tract. See also Gastrointestinal tract; Intestines: Stomach
 functional anatomy, 166-173
 glandular elements, 168
 motility, 166
 roentgenography, 168-170
 secretions, 173-181. See also Enzymes; Stomach, secretion
- Diphtheria, antitoxin passing placenta, 282, 292
 immunity, increase in, during childhood, 284
- Schick test in neonatal period, 285
- toxoid, placental transmission of protective antibodies, 281

- Ductus arteriosus, circulation through,
 fetal, 66
 closure, 66, 96
 mechanism, 68
 roentgen demonstration in sheep,
 67
 direct observation in fetal guinea pig,
 69
 patent, 96
 size at end of fetal life, 68
 Ductus venosus, closure of, 70
 Duodenum, musculature, 168
 roentgenography, 171

E

- Edema due to salt solutions, 248, 256
 of prematures, and blood proteins,
 200, 214
 and full-term infants, 248
 relation between edema and plasma
 proteins, 200, 254
 Electrocardiogram. See Heart, electro-
 cardiogram
 Electrolytes, 250-255
 and fluids, capillary permeability for,
 neonatal, 86, 97
 distribution of plasma electrolytes in
 newborn compared to child, 253
 Endocrine glands. See also Hormones;
 and under names of glands
 disturbances in mother, effect on
 child, 274
 neonatal endocrinology, 260-275
 preparations, given to prematures,
 274
 Enzymes, 173-180, 182. See also Stom-
 ach, secretion; and under names of
 enzymes
 amylase, 174
 carbonic anhydrase deficiency in fetal
 and neonatal blood, 28, 29
 disaccharide-splitting, 174
 duodenal, 174
 gastric, 174, 175, 178, 182
 hydrochloric acid, 174
 intestinal, 174
 pancreatic, 174, 178, 179
 role and development in pre-natal
 life, 173
 time of appearance, 174, 175
 Eosinophils, 114-115. See also Leuko-
 cytes
 Erythroblastosis fetalis, 289, 293
 and islet hypertrophy, 272

* See inside back cover.

- Erythroblasts. See Erythrocytes
 Erythrocytes, 103-110,*
 at birth, 229
 count, decrease in, 108
 difference in capillary puncture and
 venipuncture, 108
 effect of time of sampling, 108
 ratio of nucleated cells to leuko-
 cytes, 108, 109
 time of ligation of cord affecting
 erythrocyte and hemoglobin
 levels at birth and later, 107
 erythroblasts,*
 on first day of life, 108
 fetal, 104
 fragility, neonatal, 109
 hemolysis, 109
 of premature infants, 104
 sedimentation. See Blood, sedimenta-
 tion
 size and volume at birth, 111
 summary of changes following birth,
 112, 120-121
 Erythropoiesis. See Erythrocytes
 Estrogens, 260-266
 genital changes, in fetus produced by,
 given to mother, 265
 produced by, 263
 in, blood of male and female infants at
 birth, 263
 urine, 263
 neonatal administration, 265
 source, 264

F

- Fat, assimilation and metabolism, 207-
 213
 content of colostrum, 215
 in blood. See Blood, fat
 metabolism in newborn, 148, 149, 150,
 214, 215
 relation of type of fat in diet to fecal
 fat, 208, 209
 retention, from human milk and but-
 ter fat, 208
 in premature infants, 208
 of various fats, 208
 storage in human fetus, 210
 Feces, bacteria in, neonatal, 180
 fat, relation of type of fat in diet to,
 208, 209
 nitrogen in, 190, 192
 transitional stool, 181
 urobilin in, in newborn, 134
 Fibrinogen in blood. See Blood, fibrino-
 gen

Food. See also Diet; Nutrition
 assimilation and metabolism of specific
 food substances, 187. See also
 Carbohydrate; Fat; Protein

Foramen ovale, closure, 69

fetal, 66

G

Gasping in newborn, 57

Gastrin, 178

Gastrointestinal tract, 166-183. See also
 Colon; Intestines; Stomach
 air, distention by, 168, 182
 taken up by blood, 48
 amniotic fluid swallowed by fetus, 167
 anatomical capacity and size, 167
 anatomy, functional, 166-173, 182
 bacteria, early, 180, 181
 types, 181
 glandular structures, 168, 182
 motility, 166, 168, 172, 182
 movements in utero, 167
 ratio of mucosa to muscle, 168, 182
 roentgenography after barium, 168,
 182
 secretions, 173-183. See also Stomach,
 secretion

Genitals, alterations of external genitals
 in female, 260, 274
 premature, 260, 261

Glucose, absorption tests, 204
 in blood. See Blood, sugar

Glycogen deposits in newborn, 150

Gonadotropin. See also Hormones
 in newborn, 263

Gonococcal infection in utero, 281

H

Hay fever, antibodies in colostrum, 284

Heart, and vascular system, 77-86
 at birth, 77
 cardiac output, 89, 96
 fetal, and neonatal, 89
 cardio-thoracic ratio, 79
 electrocardiograms, 79
 chick embryos, 79
 fetal, 79
 neonatal, 79, 80
 peculiarities in T wave, 80, 97
 premature infant, 80
 enlargement, neonatal, 79
 murmurs, 80, 81, 97
 roentgenograms, 79
 shape, neonatal, 79
 size at birth, 77, 96

* See inside back cover.

Heart—*continued*
 weight, at birth, 77
 compared to body weight, 77
 of each ventricle, 78
 work of fetal and neonatal heart, 76,
 96

Hematocrit, 117*

Hemoglobin, 110-113, *. See also Blood;
 Erythrocytes
 at birth, 229
 concentration, 111, 121
 effect of time of cord ligation on, 110
 fetal, amount and quality, 29
 oxygen affinity of, 24
 persistence after birth, 27
 qualitatively different from adult,
 24, 28
 mean corpuscular, 111, 112, 121
 summary of changes following birth,
 112, 121

Hemorrhagic disease in newborn, 118

Hiccoughing respiration in newborn, 57

Hormones, 266-274
 adrenal, cortical, 266-268
 medullary, 268
 pancreatic, 270-273
 parathyroid, 272, 273
 pituitary, 273
 sex. See Sex hormones
 thyroid. See Thyroid

Hunger contractions of stomach, 171

Hydrochloric acid. See Stomach, secre-
 tion

Hydrogen ion concentration, 254, 256,*

Hypothyroidism. See Thyroid

I

Icteric index, 129, 130,*

Icterus neonatorum, 126-135
 bilirubin and, 128-135
 blood destruction and amount of
 jaundice, 131, 133
 course, 127
 icteric index, 129
 in, animals, 135-136
 prematures, 133
 twins, 134
 incidence, 126
 maturity of liver, 130-134
 onset, 127
 relation to blood volume, 134
 symptoms, 129
 urine in, 127

Ileum, peristalsis, 171-172

Immunity. See also Allergy; Antibodies;
 Antigens
 active, 284-287, 293

Immunity—*continued*

- allergy and, 289-292, 293
- colostrum and, 283-284
- non-specific "tissue immunity," 293
- passive, 281-284, 292
 - chicken pox, 282, 292
 - diphtheria, 282, 292
 - measles, 282, 292
 - mumps, 282, 292
 - pertussis, 281, 292
 - pneumococci, 282, 292
 - poliomyelitis, 282, 292
 - respiratory infections, 282, 292
 - scarlet fever, 282, 292
 - smallpox, 282, 292
 - staphylococci, 282, 292
 - streptococci, 282, 292
 - tetanus, 282, 292
 - typhoid, 282, 292
- Immunology, neonatal, 280-294. See also Immunity
- Infarcts in kidneys, 196, 197, 214
- Infection, resistance to, differences in newborn and adult, 287
- Influenza, antibacterial powers of neonatal blood, 282
- Insulin secretion in fetus and newborn, 271, 275

- Intestines, bacterial invasion, 181
 - digestion and absorption in neonatal intestine, 179
 - length, 167, 168
 - penetration by proteins, 291
 - peristalsis, 167, 168, 182
 - roentgenography, 171
 - secretion, 179
- Inulin clearance, 248
- Iodine in blood, 270
 - in thyroid in embryo, 269
- Iron, 229-231
 - daily requirement, 230
 - in liver in, newborn, 229
 - premature, 229
 - metabolism, 229
 - physiological anemia, 230
 - milk, as source of, 230, 238
 - requirements, neonatal, 238
 - storage in fetus, 229
- Isoagglutinins. See Agglutinins

J

- Jaundice in newborn. See Icterus neonatorum
- Jejunum, roentgenography, 171

* See inside back cover.

K

- Kidney, fetal, 243, 244
 - function, 243-250
 - albuminuria in newborn, 256
 - blood hydrogen ion concentration, 256
 - immaturity, 256
 - inulin clearances, 248
 - low concentration of urinary solids, 256
 - nitrogen excretion, neonatal, 193
 - osmotic pressure of urines voided by newborn, 248
 - urea clearance, 244-248
 - and rate of formation of urine, relation between, 246
 - improvement with increasing age of newborn, 247
 - in, adults and infants, 244, 246
 - full-term and prematures, 245, 246
 - ratio to inulin clearance, 248
 - water, economy, 249
 - limitation for excretion, 256
- infarcts, 196, 197, 214
- neonatal, 245-250

L

- Lactose, assimilation, in prematures, 205
- Lactation, artificially induced, 263
 - in prematures and newborn, 262
- Leprosy in utero, 281
- Leukocytes, 113-116, *. See also Eosinophils; Lymphocytes; Monocytes; Neutrophils
 - count, absolute number per cu. mm., and per cent of various white blood cells, 114
 - at birth, 113
 - of infants aged 1 to 16 weeks, 113
 - destruction and uric acid, 197
 - in premature infants, 115, 121
 - increase in newborn and role of dehydration, 116
 - inter-relationships of various white cells immediately after birth, 113, 114
 - polymorphonuclear, at birth, 113, 121
 - ratio of nucleated red cells to, 108, 109
- Lipase, early appearance in gastric secretion, 174
 - pancreatic, 174
 - at birth, 179
- Liver, digestive functions at birth, 179
 - fat and glycogen stored in fetal liver, 210, 211

Liver—continued

- inadequacy, and development of icterus, 132, 134, 135
- role in hyperbilirubinemia, 131
- vitamin A stored in, 233

Lungs, amniotic fluid in, 39, 40, 41

- atelectasis, 45-48, 58
- blood circulation in fetus, 66
- expansion at birth, 40, 42-45, 49-50, 58
- prenatal state, 9-11, 39-42
- roentgenography, 45-48
- vital capacity, 50, 53

*Lymphocytes at birth, 114-116, 121,**

M

*Magnesium retention on diet of cow's and human milk, 224**Malaria in utero, 281**Measles, antibodies in newborn, 282, 292**at birth, 281**Meconium, amount at birth, 179*

- bacteria in first discharges, 181
- time of appearance, 183
- type of organism, 181
- bilirubin in, 130, 131
- composition, 179, 182
- disappearance, 179
- passed in utero, 167, 179

*Metabolism, caloric requirements, 151-152, 162**carbohydrate, 200-207**energy, 138-153**and body surface, 142-144**and body weight, 141-142**of fetus, 138-140**of prematures, 144-147, 152, 161**muscular activity and, 143, 145, 151, 161**pulse rate and, 88**temperature and, 153**fat, 207-214**nitrogen, 187-200**respiratory quotient, in fetal metabolism, 149**in newborn, 148-151**2-Methyl-1,4-naphthoquinone and prothrombin content, 118**Milk, calcium in human and cow's milk, 222-225**fat retention on human milk, 208**iron in, 230**phosphorus in cow's and human milk, 228**Milk—continued**riboflavin in cow's and human milk, 236**vitamin, A in human and cow's milk, 234**C in human and cow's milk, 236**D in human and cow's, 232**"witches," 262**Mineral metabolism, 221-231**reserves of newborn, 237**retention, effect of diet on, 222-225, 237-238**Monocytes, 114, 115,***Mortality rate, infant, 4-5**Mumps, antibodies in newborn, 282, 292**Myelocytes at birth, 113-114*

N

*Neutrophils, polymorphonuclear, 113-116,***Niacin, 236, 239**Nikethamide in asphyxia, 35**Nitrogen, absorption, 190**in premature infants, 191**amino acid, in blood, 191**balances, 191-193**equilibrium, 192**in, blood. See Blood, nitrogenous substances**feces, neonatal, 190**urine. See Urine**metabolism, 187-197**fetal, 190**pure, effect of inhalation on dogs, 36**retention in prematures, 193**on diet of cow's and human milk, 224**Nutrition, fetal and neonatal, 187-214.**See also Diet; Food; Vitamins*

O

*Olive oil in feeding prematures, 216**Ovaries of newborn infant, 261**Oxygen, absorption through skin, 48, 49**consumption, and body surface, 54**as index of metabolism during human development, 140**deficiency; anoxia at birth, 33-39**anoxia in onset of respiration, 34**effects and duration of anoxia at birth, 35**in newborn, 33**effect on later life, 35, 39, 58**pulsation in cord vessels in anoxia, 72**in blood. See Blood, oxygen**supply of fetus, 14, 15, 18-21*

* See inside back cover.

P

- Pancreas, enzymes at birth, 179
 relation between age and digestive activity and quantity of, 180
 fetal, 270
 hypertrophy and hyperplasia, fetal, in infants of diabetic mothers, 272
 insufficiency in mother, 275
 insulin secretion, 271
 lipase, 174
 secretion, at birth, 179
 trypsinogen, 174
- Panting in newborn, 57
- Parathyroid hormone, 272, 273
 effect on fetus, 273
 physiological hypoparathyroidism, 228, 237
 secretion, neonatal, 273
- Parotitis. See Mumps
- Pepsin, time of appearance in fetal gastric secretion, 174
- Perspiration in premature, 157
- Pertussis. See Whooping cough
- Phosphatase,*
 activity in bone, 229
 serum or plasma at birth, 228
- Phosphorus, in blood. See Blood, phosphorus*
 in cow's milk and human milk, 228
 metabolism, 221, 227
 retention on diet of cow's and human milk, 224, 237
- Pituitary gland, 273
 gonadotropic hormones and anterior pituitary-like substance of pregnancy urine unable to pass placenta, 264
- Placenta, assays for androgens at term, 266
 blood vessels, response to oxygenation of blood, 71
 volume at birth, 74
 at different periods, 73, 74
 total, 73
 circulation, 73
 fetal blood in placental circuit at end of gestation, 75
 nutritional function, 199
 transfer, antifibrinolysin, 282
 antigens and antibodies, 280, 281, 282
 protein molecules acting as antigens, 290
 skin-sensitizing antibodies, 290, 291
- Placenta—*continued*
 transfer—*continued*
 antistreptolysin, 282
 calcium, 273
 glucose, 271
 hormones, 268
 adrenal cortical, 268
 pancreatic, 272
 parathyroid, 273
 thyroid, 269
- Plethysmograph, body, to measure respiration rate, 51
- Pneumococci, antibacterial powers of neonatal blood, 282, 292
 infections in utero, 281
- Poliomyelitis, antibodies in newborn, 282, 292
 not transferred to fetus, 281
- Potassium at birth and in neonatal period, 252
 in blood. See Blood, potassium*
 retention on diet of cow's and human milk, 224
- Premature infants, acid-base equilibrium in, 255
 acidosis, 253, 256
 ascorbic acid, 234, 235
 blood, bilirubin in, excessive, 130, 133
 calcium measurements, 237
 deficiency of carbonic anhydrase in, 28, 29
 distribution, 81, 82
 fluctuations in prothrombin time, 119
 nitrogenous substances in cord blood, 189
 platelets, 116
 pressure, 91, 95, 97
 proteins, 198, 214*
 serum globulin, 286*
 sugar, 203, 205, 215
 and birth weight, 202
 total and fractional serum proteins, 199*
 transfusion of adult blood, 29
- breast secretion, 262
 calcium, retention, 224
 skeletal, 226
 caloric requirements, 152, 162
 capillaries, 83, 85
 carbohydrate metabolism, 148, 149, 150
 chloride ion variation, 252
 creatinuria in, 195, 196
 edema, 248
 and blood proteins, 199, 200, 214
 electrocardiograms, 80

* See inside back cover.

- Premature infants—*continued*
 endocrine therapy, 265, 274
 enzymes, 174
 erythrocytes, 104, 120
 number of, 105, 106
 fat retention, 208, 216
 food, rapidity of passage, 172, 182
 hunger contractions, 171
 iron in liver, 229
 jaundice in, 130, 133, 135
 kidney function; urea clearance in, 245
 lactose assimilation in, 206
 leukocytes, 115, 121
 metabolism, 138, 144, 147
 compared with normal adults, 145
 oxygen consumption as index, 140
 respiratory quotients, 150
 summary, 161
 nitrogen, absorption, 191
 metabolism, 193
 nitrogenous substances in cord blood, 189
 retention in, 193
 ovaries, 261
 respiration, as related to body surface, 54
 body weight, 53
 rate and depth of breathing, 52, 53, 59
 rhythms, 55-57, 59
 thorax and diaphragm in, 49, 58
 volume, 53
 rickets in, 232
 size, relative, 4
 stomach acidity, 174-176
 temperature, 154, 156-161, 163
 thyroid activity, 270
 vaginal discharge in, 260
 vasomotor reaction, shivering and perspiration in, 157
 vitamin D requirements, 231, 232, 238
 Prolactin in urine, 264
 Prostate, effect of estradiol on, 263
 of fetus or newborn, 261
 Protein, digestibility, 190
 in, blood. See Blood, proteins
 colostrum, 191
 metabolism, 187-200
 and nitrogenous substances in blood, 193
 summary, 214
 penetration through intestinal wall, 291
 Prothrombin. See Blood, coagulation
- * See inside back cover.
- Pseudo-hermaphrodisism, adrenal cortical enlargement in, 267
 Pulse rate, 86-89,*
 and circulation time, 90
 during minimal metabolism, 88
 instability, neonatal, 88
 Ptyalin in saliva, and starch digestion 180
 in fetus, 174
 Pyruvic (pyroracemic) acid excretion, 255
- R
- Rennin, time of appearance in fetal gastric secretion, 174
 Respiration, 7-59
 and blood; carbon dioxide and asphyxia, 34
 dissociation curve of human fetal blood at birth, 22, 23
 effect on fetus, 16
 in blood at and before birth, 21-23
 in fetus at or near term, 21
 carbonic anhydrase deficiency in fetal and neonatal blood, 28
 circulatory interruption in releasing respiratory activity, 15, 16
 effect and duration of anoxia at birth, 35-39
 fetal, and neonatal characteristics affecting respiration, 28
 gases, and fetal activity, 13-18
 of animal and human subjects at and before birth, 20
 hemoglobin, fetal, qualitatively different from that of adults, 24
 oxygen, at onset of, 19
 and carbon dioxide economy of human fetus, 18-22
 dissociation curves in infants after birth, 27
 of goat fetus and its mother, 25
 of infants at birth, and pregnant and normal non-pregnant women, 26
 oxygenation, fetal, 14
 post-natal oxygen adjustment of arterial blood, 37, 38
 respiratory peculiarities of fetal blood, 22
 tolerance of anoxia in newborn, 35
 as related to body, size, 53
 weight, 53
 carotid and aortic reflex mechanisms, 34, 57
 chemical stimulus, result of, 15

Respiration—*continued*

- Cheyne-Stokes, 55, 56
- clinical, manifestations, 45-50
 - summary, 57
- cog-wheel, 55, 56
- cutaneous, 49
- effect of anesthesia and trauma on, 58
- gasping, 57
- hiccupping, 57
- inspiratory force available to new-born, 44
- intra-uterine respiratory movements, 7-11. See also Respiration and blood
 - animal experiments, 7-18
 - "apneic," 12
 - chemical, measurements, 14
 - regulation in, cats, 17
 - small animals, 16
 - chronological and individual inconsistency, 11
 - chronology of fetal respiratory activity in man, 13
 - clinical summary, 28
 - depressed by anoxemia, 16
 - effect of, clamping umbilical cord, 12, 16
 - sedative and anesthetics given to mother, 11
 - effect on fetal and neonatal lungs, 39
 - fetal movements of respiratory muscles, 8-18
 - preparatory to extra-uterine breathing? 10, 11
 - transilluminated fetus in utero, 12
 - when placental interchange is interrupted, 13
- lung; amniotic fluid in lungs, 41
 - expansion at birth, 42, 58
 - roentgenograms of sites of earliest inflation, 45
- mechanical forces, 42-45
- onset at birth, 33
 - anoxia, 31
 - carotid and aortic chemo-receptors, 34
 - circulatory interruption necessary for, 15, 16
 - effect on blood pressure, 91
 - medullary center, 35
- panting, 57
- periodic, 55-57
- rate, 50-52,*
 - and depth of breathing, 59
 - average, 59

* See inside back cover.

Respiration—*continued*

- rate—*continued*
 - in prematures, 51, 52, 59
 - volume and regularity in neonatal period, 50-57
 - reflex regulation of breathing, 34
 - resuscitating devices, mechanical, 44, 58
 - rhythms of normal full-term infants, 50, 55, 56
 - kymograph tracings showing, 55
 - suspended at birth, 35, 58
 - survival after, 58
 - thorax, and diaphragm in, 49, 58
 - changes, 49
 - vital capacity, 50
 - volume, 50, 51, 52, 53, 59,*
 - and body surface, 54, 58
 - in prematures, 53
 - maximum, during first ten days of life, 52
 - Respiratory tract, infections, neonatal resistance, 282
 - Resuscitating devices, mechanical, 44, 58
 - Reticulocytes,* . See also Erythrocytes
 - at birth, 109
 - on first day of life, 108
 - Riboflavin, 239
 - in cow's milk, 236
 - Rickets and vitamin deficiency, 231, 232
 - in prematures, 237
 - prevention, 237
 - rare, at birth, 232
 - vitamin D in prevention, 238
 - Rubner's law, 141
- S
- Saliva, in fetus, 174, 180
 - ptyalin in, 174
 - and starch digestion, 180
 - Salt solutions, edema due to, 248, 256
 - Scarlet fever, antibacterial powers of neonatal blood, 282
 - Schick tests in neonatal period; 285
 - Sedimentation time, 120,*
 - Sex, hormones, 260-266. See also Androgens; Estrogens; Gonadotropin; Prolactin
 - given to prematures, 265
 - of unborn affected by administration of estrogens and androgens, 265
 - Shivering in prematures, 157
 - mechanism, 153, 154
 - Skin, absorption of oxygen through, 48, 49
 - capillaries, 83-85

Skin—continued

- color in early life, 126
- negative pressure, amount borne without signs of capillary damage, 85
- Smallpox, antibodies in newborn, 282, 292
- at birth, 281
- vaccination, effect of age on, 285
- Sodium concentration in plasma, 251, 253,*
- retention on diet of cow's and human milk, 224
- Staphylococcal antitoxin, 282
- Starch digestion and ptyalin in saliva, 180
- Stomach, acidity. See also Stomach, secretion
 - and blood, 177
 - free and total gastric acidity, 175, 176, 177
 - germicidal action, 178
 - hydrochloric acid, 174-178
 - of premature infants, 176
 - total acidity of gastric juice during first month of life, 177
- air in, and size of stomach, 169, 173
- anatomy, cross-sectional, 168
- capacity, neonatal, 167, 182
- emptying time, 169
 - in newborn, 170
 - of human, and cows' milk, 170
 - time of identifying feedings in feces, 172, 182
- enzymes. See Enzymes; Stomach, secretion
- hunger contractions, 171
- motility, 170, 173
- musculature, 168
- peristaltic movements, 169, 170
- position, variations, 169
- roentgenograms, 169
- secretion. See also Stomach, acidity
 - amount of gastric juice at birth, 175
 - amylase in fetus, 174
 - early digestion, 179
 - enzymes, 182
 - in fetus, 174
 - role and development of enzymes in pre-natal life, 173
 - time of appearance of various enzymes, 174, 175
- gastrin, 178
- lipase in fetus, 174

Stomach—continued

- secretion—*continued*
 - pepsin, and rennin, 178
 - pepsin, hydrochloric acid, and rennin, 174
 - shape, variations, 169
 - size, 169
- Stools. See Feces
- Streptococcal infections, antibacterial powers of neonatal blood, 282
- Sugar, in blood. See Blood, sugar
- in urine. See Urine, sugar
- Sulfur retention on diet of cow's and human milk, 224
- Sunlight and vitamin D, 232
- Suprarenal glands. See Adrenals
- Surface. See Body surface
- Syphilis in utero, 281

T

- Tauch reflex, 39, 40
- Temperature (body), 153-163
 - at birth, 154, 162
 - chemical regulation of, 153
 - clinical summary, 161
 - correlation between body temperature and total metabolism, 153
 - diurnal rhythms of neonatal life, 161
 - effect of change in environmental temperature, 157, 158
 - low, better than fluctuation in premature infant, 163
 - normal infants during first 8 hours, 154, 155
 - physical regulation, 153
 - post-natal 3 degree fall, 155
 - response of prematures to external changes, 156-158
 - return to normal after chilling, 156
 - stability, early, 155, 156
 - subnormal, 145
 - in premature, 157
- Testicle, internal secretion. See Androgens
- Tetanus, antitoxin, transfer to fetus, 282, 292
- Tetany, 226, 227, 273
- Thiamin, 239
 - in cow's milk, 236
- Thorax, 45
 - cardio-thoracic ratio, mean, in first 3 weeks, 79
 - development, neonatal, 49
 - roentgenograms, 45, 46
 - size, variability, 79
- Thyroid activity during human neonatal period, 270

* See inside back cover.

- Thyroid—*continued*
 deficiency in mother, 275
 hormone, fetal, 269
 transmission from mother to fetus
 or in reverse direction, 269
 hypothyroidism, fetal, 269
 morphology at birth, 268
 Thyroxine, in embryo, 269
 Tidal air, 51, 59,*
 Transitional stools, 181
 Trypsinogen in gastric secretion, 174
 Tuberculosis in utero, 281
 Twins, icterus neonatorum in non-
 identical and identical twins, 134
 rickets in, 232
 Typhoid bacillus "H" agglutinins in
 blood of newborn, 282

U

- Umbilical cord, bleeding from, 72
 effect of temperature and handling
 on, 72
 post-natal, 71, 96
 blood, antibodies in, 280, 282
 bilirubin in, 128, 129
 calcium, 226
 carbon dioxide dissociation curve,
 23
 clotting in, 73
 fats in vein and artery, 210
 fibrinogen, 120
 nitrogenous substances in, 189
 oxygen dissociation curves, 25
 level in average umbilical arterial
 and venous blood, 71
 platelets of normal infants, 117
 sedimentation time, 120
 sodium value of serum, 251
 sugar, 202
 thyroid hormone in, 270
 total and fractional serum proteins
 in artery and vein, 199
 uric acid in, 196
 vessels at birth, 70
 mechanism for terminating flow
 through vessels, 73
 vitamin, A and carotene in, 233
 C in, at birth, 235
 blood pressure in artery, 92, 97
 effect of tying cord, 91
 ligation, 70, 71, 96
 time, 73
 effect on, blood pressure, 91
 blood volume and red cell mass,
 76
- Umbilical cord, ligation—*continued*
 time, effect on—*continued*
 development of icterus, 134
 erythrocyte count, 107
 hemoglobin, 110
 uric acid excretion, 197
 vein, changes in content, 71, 72
 Urea clearance. See Kidney, function
 in blood. See Blood, urea
 Uric acid, in blood. See Blood
 in urine. See Urine
 Urine, albumin in. See Albuminuria
 amino acids in, 188, 191
 androgen in, and sex of infant, 265
 creatinine in, 188, 195
 creatinine in, 188, 195
 estrogens in, 263
 excretion, average, 249
 formation and urea clearance, rela-
 tion between, 246
 in fetal bladder, 243
 nitrogen, 188, 192-194, 214
 osmotic pressure of, voided by new-
 born, 248
 prolactin in, 264
 pyruvic acid excretion, 255
 sugar, 206
 glucose absorption tests, 206
 urea. See Kidney, function
 uric acid, 214
 average daily excretion per kilo-
 gram of weight, 196
 urobilin content of newborn, 134
 Urobilin in urine, 134
 Uterus, in newborn, 261

V

- Vaccination, smallpox, 293
 Vagina, discharge in newborn, 260
 hypertrophy of epithelium, 261
 Van den Bergh reaction, 130
 Virilism, adrenal, 267
 Vital capacity, 50
 Vitamin, A, 232-234, 239
 in, fetal liver, 233
 fish-liver supplement of vitamin
 D, 234
 liver at birth, 233
 requirement of newborn, 234, 239
 slow removal from liver, 234
 B, complex, 236, 239
 C (ascorbic acid) at birth, 234, 236, 238
 fall after birth, 238
 in, cord blood at birth, 235
 human and cow's milk, 236, 238
 liver, 235

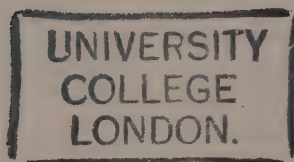
* See inside back cover.

Vitamin C—*continued*

- increases with length of gestation, 235
- optimum requirement of newborn, 236
- D, 231, 232
 - and sunlight, 232
 - in, milk, 232
 - prevention of rickets, 238
 - maternal source, 231
 - plus cow's milk, diet for retention of calcium and phosphorus, 237
 - supplementary to feeding, 232
- deficiency and rickets, 231
- K, and blood coagulation in newborn, 117-119
 - obstetrical use, 119
 - source, 119
 - to mother or child, 118, 121
- metabolism, 231-236
- reserve of newborn infant, 237

W

- Water, content of embryo, fetus and newborn, 249
- control of electrolytes and, 250
- regulation, 243
- Weight, as related to respiration, 53
 - at birth and blood sugar in pre-matures, 202
 - average daily excretion of uric acid per kilogram of, 196
 - body weights and body surfaces at various ages, 142
 - data indicating relation of increasing weight to basal metabolism, 146
 - "physiological loss," 249, 256
- White blood cells. See Leukocytes
- Whooping cough, resistance not transferred to infant, 283
- vaccination, effect of age, 285
- vaccine, placental transmission of protective antibodies, 281
- "Witches' milk," 262



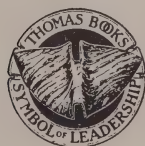
This Book

THE PHYSIOLOGY OF THE NEWBORN INFANT

A Second Printing

By CLEMENT A. SMITH, M.D.

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NORMAL VALUES

Normal values useful for reference purposes have been selected from the text and listed below. Since investigators have used various periods for sampling, all data cannot be given for each day of neonatal life. A single figure extended over several days usually indicates absence of a significant trend during that period. Ranges are given in parentheses below the averages or means. For further discussion and references to authors here quoted, see appropriate sections of the text.

	At birth	1st day	2nd	3rd	4th	5th	6th	7th
Respiration:								
Rate/minute		41 (27-82)	43 (27-82)			41 (25-70)		
Tidal air (cc.)		19 (10-27)	18 (12-25)			19 (15-26)		
Circulation:								
Resting pulse rate	180	124 (100-175)						127 (100-175)
Blood pressure	80/46	82/40			92/50			
Blood volume (as % of body wt.)				9.6% (8-13.8)				
				12.1% (8.2-16.2)				
Blood morphology:								
Erythrocytes (millions)	4.8 (3.8-6.0)	5.25 (3.8-7.6)				5.3 (3.6-7.6)		
Hemoglobin (gm.)	17.9 (13-22)					19.0 (15-25)		
Mean r.b.c. size (μ^2) Ave. (Range of means)	113 (90-124)					107 (90-124)		
Erythroblasts (per 100 nucleated cells)	7 (0-15)	1.5 (0-13)				0.2		
Reticulocytes	5-6%							
Hematocrit	51.7 (48-55)	57.2 (51-63)		65 (58-71)			55 (49-60)	
White blood cells:								
Total ($\times 1000$)		24.9 (15-45)			10.6 (4-18.8)			10.4 (7.6-16.4)
Polymorph. neutrophils (%)		68.7 (53-82.5)			45.2 (32-59)			39.2 (26.5-67)
Lymphocytes (%)		13.3 (9-36)			29.6 (15-44.5)			40.7 (17-61)
Monocytes (%)		6.5 (3-11.5)			16.9 (10-23)			14.3 (7-19.5)
Coagulation:								
Platelets ($\times 1,000$)	227 (140-290)							233 (160-320)
Prothrombin (% of adult normal)		85 \rightarrow 70	20	50	70	100		
Coagulation time (minutes)	2.5 (2-3)	5.5 (2-9)	6	5.5 (3-12)			3.5 (2-5)	
Bleeding time (minutes)	2							
Sedimentation time (hours) (Linzenmeier method)								
		106 (30-185)	57 (3-180)		45 (6-120)		20 (5-96)	
Nitrogen and protein metabolism:								
Blood urea N (mg.)	15.0 (10-22)			16.0 (12-20)		15.0 (9-18)		
Blood non-protein N (mg.)	35 (24-64)				45 (25-62)			
Blood uric acid (mg.)	3.1 (2.4-5.0)	3.6 (2.7-5.1)	3.7 (2.5-4.7)			2.9 (2.1-3.7)		
Serum protein (gm.)	6.04 (5.15-7.43)	6.03 (5.1-7.0)		5.9 (5.15-6.67)		6.0 (5.1-7.0)		5.93 (5.1-6.6)
Serum protein and fractions:								
Total protein		5.11						
Albumin		3.76						
Globulin		1.34						
Blood glucose:								
	104	68 (47-102)	70 (52-103)	76 (57-110)				
Blood (plasma) fats:								
Total lipids (mgm./100 cc.)		221 (119-331)						
Neutral fats (mgm./100 cc.)		80 (8-149)						
Phosphatids (mgm./100 cc.)		27 (0-94)						
Free cholesterol (mgm./100 cc.)		32 (23-44)						
Cholesterol esters (mgm./100 cc.)		82 (47-128)						
Electrolytes:								
Total base (meq./L.)						152.4		
Sodium (meq./L.)						144.0		
Potassium (meq./L.)								
Chloride (meq./L.)						106.9		
Bicarbonate (meq./L.)						22.1		
CO ₂ content, venous serum						52.1 Vol. %		
pH, venous serum						7.4 (7.27-7.47)		
Calcium, Phosphorus, Phosphatase:								
Serum Calcium (mg./100 cc.)	11.3 (7.3-16.9)		9.93 (7.2-12.3)			10.45 (7.5-13.9)		
Serum Phosphorus (mg./100 cc.)	5.55 (4.2-8.0)		6.08 (3.7-8.6)			5.93 (3.5-7.6)		
Serum Phosphatase (Bodansky units)			7.1 (4.4-9.8)					
Pigments:								
Serum bilirubin (mgm.) Median (Range)	1.6 (0.4-3.9)	3.2 (1.4-6.0)	5.0 (1.5-9)	4.8 (1.3-11)	4.5 (1.2-12.8)	3.9 (0.9-12.5)	3.8 (0.9-12)	3.4 (0.9-10.8)
Icterus index	12	26	33	42	45	53	41	44

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8th	9th	10th	11th	12th	13th	14th	Later	Source of data
	49 (32-80) 21 (13-27)					133 (100-175)		Deming & Washburn Deming & Washburn Vierordt; Benedict & Talbot Woodbury, et al.; Dexter & Weiss De Marsh, et al.
		100/54					Age 2 months 3.8 (2.5-5.3) 12.1 (8.5-18) 92 (75-115)	Birth figure—ave. 8 latest studies. Other data from Guest et al. Guest
		0.5%						
	54 (48-60)		48 (43-52)					Bruch & McCune; Hurwitz et al. Forkner
		12.8 (8-16.5) 28.9 (18.5-46) 49.1 (22-69) 17.1 (8.5-28)						
						242 (170-370)	Age 1 month 277 (200-370)	Merritt & Davidson Grossman Sanford Sanford Hurwitz et al.
				3.0 (2-5) 2-3 10 (4-24)				Lichtenstein; Sherman et al. Miller; Sedgwick and Zeigler Kingsbury & Sedgwick
	14 (4-37)	13 (3-23)						Denzer et al. Rapoport et al.
				34 (22-50)				
		1.6 (1.1-3.5)						
							Prematures (1-68 days) 4.55 3.55 1.01 Adults (same method): 70-90	Older infants (2-11 months) 6.10 4.97 1.38
							Children 7.30 5.00 2.40	Ketteringham & Austin Seann and McNamara
	468 (297-651) 173 (92-268) 103 (19-190) 51 (37-68) 142 (103-189)						Adults 735 (450-1260) 225 (50-580) 151 (60-335) 82 (56-121) 247 (86-440)	
								Marples & Lippard Bruch & McCune McCance & Young Marples & Lippard Marples & Lippard Marples & Lippard Marples & Lippard
				7.8				Todd et al. Todd et al.
							2-6 weeks 10.4 (7.3-13.5)	Barnes & Munks Davidson et al. Bonar
		8.9 (6.6-11.1)						
2.7 (0.6-10.2) 35	2.8 (0.5-9.9) 28	2.5 (0.4-8.2) 29						

